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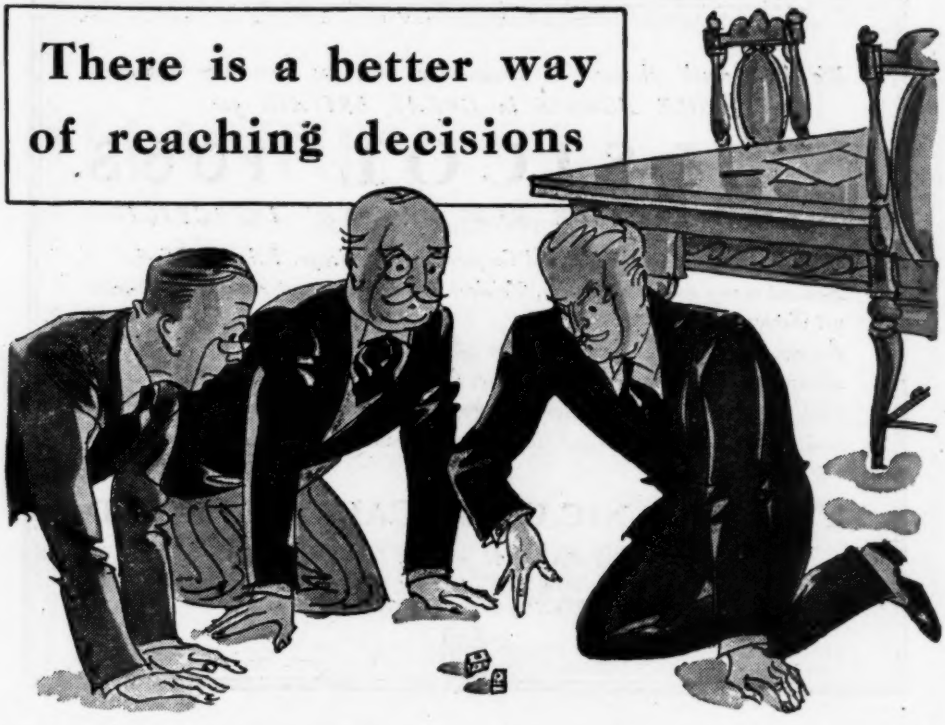

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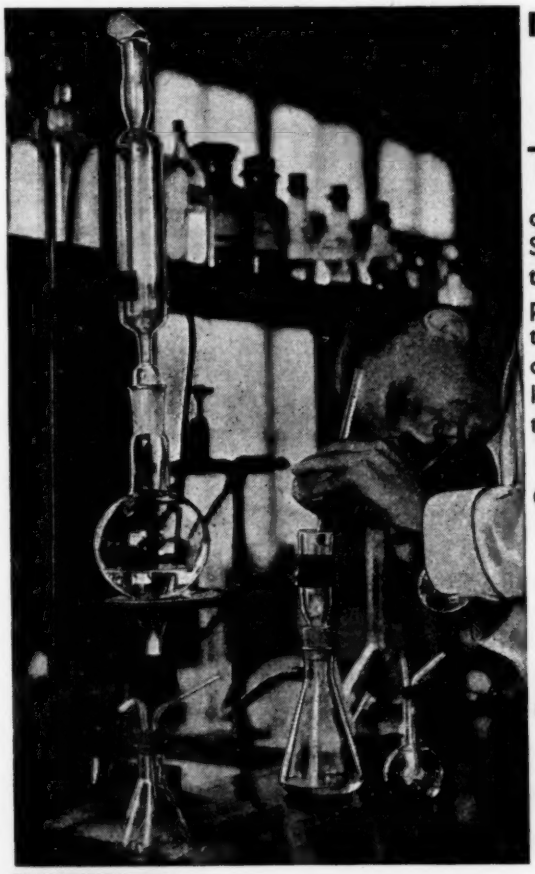

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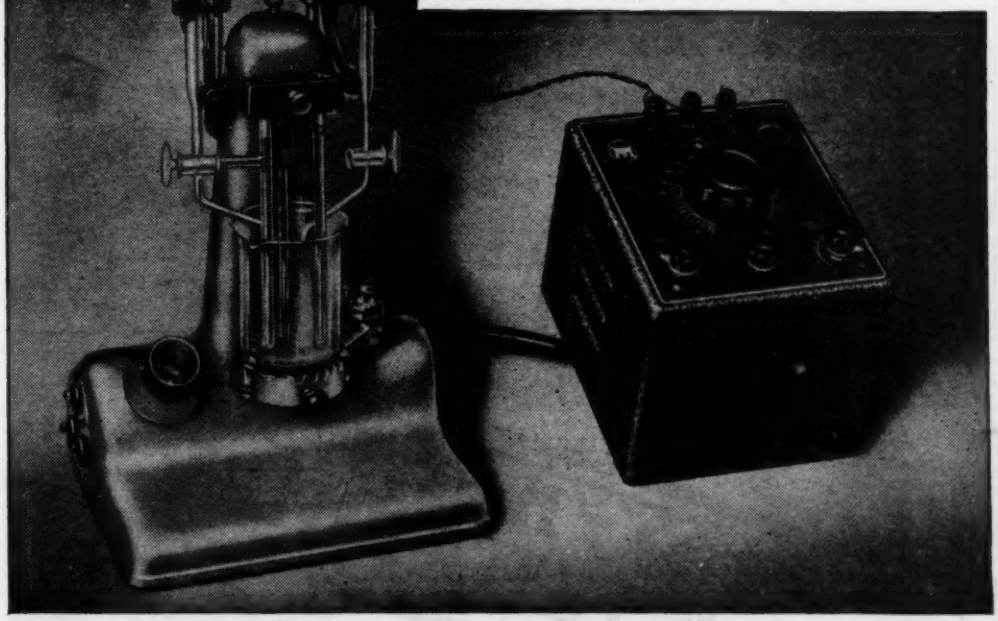

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In 1914 Rutherford's work was rudely interrupted by the War, and for the next four years he was engaged on work of immediate national importance. He got back to his own work in 1918 with renewed vigour and started at once to attack the structure of the nucleus, a problem which he had said a few years back must be left to the next generation. His efforts were quickly rewarded. Within a year he proved unmistakably that nitrogen was destroyed by alpha particles and that hydrogen was a product. From that day to this there has been a continuous and almost bewildering addition to our knowledge of the structure of the nucleus and of the transmutation of the elements. The pace was quickening even at the end of Rutherford's life. Many of the results are of no direct interest to chemistry except in so far that every advance in fundamental physics is bound to affect chemistry. What is of special interest is the discovery of heavy hydrogen and of neutrons, and the production of artificial radioactivity by neutrons and by other methods. The discovery of heavy hydrogen, or deuterium, and of the neutron, followed one of the most remarkable predictions in the history of science. " It seems very likely," said Rutherford in his Bakerian Lecture in 1920, " that one electron can also bind two H nuclei and possibly also one H nucleus. In the one case this entails the possible existence of an atom of mass nearly 2 carrying one charge, which is to be regarded as an isotope of hydrogen. In the other case, it involves the idea of the possible existence of an atom of mass 1 which has zero nuclear charge. Such an atomic structure seems by no means impossible. . . . Such an atom would have very novel properties. Its external field would be practically zero, except very close to the nucleus, and in consequence it should be able to move freely through matter. Its presence would probably be difficult to detect by the spectroscope, and it may be impossible to contain it in a sealed vessel. On the other hand it should enter readily into the structure of atoms, and may either unite with the nucleus or be disintegrated by its intense field, resulting possibly in the escape of a charged H atom, or an electron, or both." It was after some years and many abortive trials that this prediction was fulfilled. Neutrons were discovered in 1932 and heavy hydrogen in 1933. In the same year the first artificial radioactive element was discovered, " which showed," said Rutherford, " how little we know about radioactivity." The properties of neutrons were found to be just as Rutherford predicted, and the last few years have seen the production of radioactive varieties of the large majority of known elements. Every year adds to their number, and what one says today is liable to become out of date tomorrow. To the chemist, and particularly perhaps to the bio-chemist, these radioactive elements provide a means of experimental attack on problems which have hitherto been out of their reach.

So we can summarise Rutherford's influence on chemistry in the following way. By his early work on the disintegration of elements he destroyed the chemist's conception of the nature of atoms, and in doing so gave the atomic theory of matter a reality which it never had before. By his work on the scattering of alpha rays he removed the blots on the periodic system by removing its foundation and replacing it with something better. In so doing he caused the development of a new and fruitful conception of valency. By his work on the transmutation of elements he opened up an immense field of experimental work for the chemist, a field which few can doubt will yield results of the utmost importance to biology as well as to chemistry.

The secret of Rutherford's success in inspiring others lies not only in his genius but in his unselfishness. Surely there never was a great man who gave so much credit to others. This was not a quality of his later years when his reputation was established and could not possibly be affected by anyone else's reputation. It was a quality that he had from the very beginning. In his report on the thesis which Rutherford submitted when he was an applicant for the 1851 Exhibition, Professor Gray drew attention to some of Rutherford's results which were not new, but added : " As the author is most careful to acknowledge his indebtedness to others I feel sure he arrived at his conclusions independently." It was that quality that endeared Rutherford to his associates, that brought him loyalty and affection as well as admiration. He would always do anything he could to encourage others. In his last published lecture at Cambridge he said : " Scientists are not dependent on the ideas of a single man, but on the combined wisdom of thousands of men, all thinking of the same problem and each doing his little bit to add to the great structure of knowledge which is gradually being erected." There spoke the genuine Rutherford. It was for this co-operation that he worked all his life, and it was this that was not the least of his achievements.

I have heard it said that it was a pity that Rutherford had no Boswell, that no one of the many men who worked in daily contact with him made notes of his ways, of his sayings, of his few mistakes as well as his many successes, of his manners, good and bad, and of his faults as well as of his virtues. I share the feeling. His name will live for ever in the history of science, and yet one would like to feel that Rutherford himself lived in the history of our times as no man of science has ever lived before. In many ways Rutherford was indeed very like the great Dr. Johnson. He came to dominate the scientific world of his time in exactly the same way as Johnson had dominated the literary world. Like Johnson he had a deliberate and strong utterance and loved to fold his legs and have his talk out. Like Johnson he had occasional sallies of heat of temper and at times of passionate unreasonableness. He was the centre of attraction at any scientific gathering, and especially at the dinners of the Royal Society Club where some of us used to hang about in the hopes of hearing him say, " come and sit by me." Then just as people were always a little frightened of Johnson so I think we were a bit frightened of Rutherford, not because he could or would do us any harm but because we might fall short of his own standard of work and conduct. Of course, the shortcomings were there, but we preferred him not to observe them. Like Johnson, too, he never considered whether he should be a grave man or a merry man, but just let inclination for the time take its course. He had a boisterous sense of fun and a loud laugh. By precept and by example he helped to keep our minds free from cant. He hated pomposity

and artificiality. He loved simple people, and simple ways, and lived a simple life. He brushed little annoyances aside.

But in other respects he was very unlike Johnson. Poor Dr. Johnson suffered from ill health all his life, and was subject to severe fits of depression. Rutherford had abounding health and vigour, and there can hardly ever have been a man of such intellectual power who was so little subject to mental depression. So if we can find similarities we can also find great contrasts. Johnson lived on the whole a life of laziness interrupted by periods of feverish activity to which he was driven by lack of money. Rutherford was at the top of his form at breakfast, a thing that weaker men affect to despise, and lived a life of feverish intellectual activity relieved by short periods of magnificent idleness. When he took a holiday it really was a holiday.

There is another curious contrast with Johnson. Whereas Dr. Johnson used to relieve his literary labours by doing chemical experiments and by talking science, so Rutherford used to relieve his scientific labours by a study of literature. In his early days he was a great novel reader. When he was at Montreal, working long hours in the laboratory, the librarian found it difficult to supply him with enough light literature for his leisure moments. But later on in life he gave up the reading of novels or any form of imaginative literature, and confined himself to history and biography, to books that dealt with facts. I think he must have surprised many people from time to time by his knowledge of ancient history. He had a retentive memory, and an absurdly entertaining way of burlesquing hackneyed quotations or common proverbs, as for instance on one occasion when we were discussing short-lived reputations of men who rashly announced discoveries which were soon detected as false, he said: " Well, 'tis better to have boomed and bust than never to have boomed at all."

He took great pains in making his written papers clear and concise; they are models of what scientific papers should be. But although his writings were uniformly good and clear, Rutherford was never a good speaker except on his own subject. On formal occasions, or when he had to speak extempore, he would hesitate, fumble for words, and repeat himself. When he had to make an official speech with notes perhaps supplied by others, those who knew him well would fidget in their seats, waiting for the time when he would put the notes aside and say to himself, almost audibly, " now let's tell them about something interesting," and become himself again. But when he lectured about his own work he was superb, and unique. I expect that all who have heard him have their own private memories of him. I can almost see him now, standing in this famous lecture room, massive and commanding, demonstrating to an enthralled audience the transmutation of matter by high speed protons and deuterons. A train of valves amplified the effect of the transformation of a single atom to such an extent that it could operate a counter within sight and sound of the audience. He showed first the transmutation by protons. The counter ticked slowly as the process went on. " Now," said Rutherford, " if you will allow me, we will bombard the same target with deuterons, and I think you will observe a greatly accelerated rate of transformation." The assistants made the necessary adjustments and the current was turned on again. The counter ticked if anything rather more slowly than before, and the audience began to titter. The assistants came forward to see what was wrong. " No," roared Rutherford defiantly, " leave it alone." The words were hardly out of his mouth when the ticker obediently went off with a rush, and the audience dissolved into laughter and cheers. I was told afterwards that some of the valves used were sensitive to sound.

I hope that you will not think my stories of Rutherford unsuited to the occasion, and disrespectful to his memory. For my part I feel cheerful when I think of him, and glad to have lived in times that he made so intensely interesting; and I do not think he would wish us to be too solemn when we meet to commemorate his life and work. Besides, what I wished so much and have tried to do, was to bring back to you for a few moments the real Rutherford, as he was, his features unobscured by a smooth mask of panegyric. Of course he knew he was a great man. All his life he was like a young man rejoicing in his strength. He enjoyed, unaffectedly, the many honours that came to him, and cabled the news of each one, as it came, to his mother in New Zealand, the evening of whose long life was gladdened by the fame of her son. There was no false modesty about Rutherford; but neither was there any vanity. He never seemed to be driven by the very human motive to excel other men. His compelling passion was the search for truth.

" Well, it's a great life," Rutherford often used to say, in high spirits. It was, indeed, a great life. Happy stories will be told of him till death takes away the last of those who knew him well.

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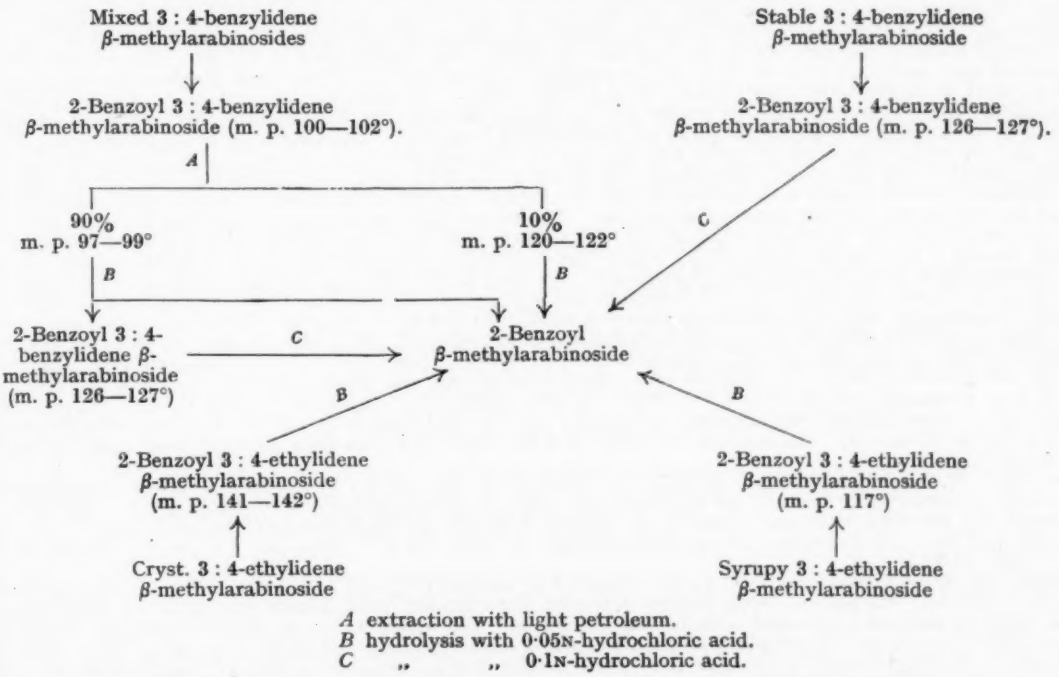
211. *Reactions of β-Methylarabinoside. Part I. 3 : 4-Benzylidene and 3 : 4-Ethylidene β-Methylarabinopyranoside.*

By Mary Ann Oldham and John Honeyman.

When benzaldehyde and β-methylarabinoside are heated together, a syrupy mixture of the two possible 3 : 4-*benzylidene β-methylarabinopyranosides* is obtained. The two forms are distinguished by the difference in the stability of the benzylidene group in the isomeric 2-*benzoyl* 3 : 4-*benzylidene β-methylarabinosides*. The preparation of 2-*methyl arabinose* is described. Paraldehyde and β-methylarabinoside give a syrupy mixture of the two 3 : 4-*ethylidene β-methylarabinopyranosides* from which one form can be separated in the crystalline state. No difference in the stability of the ethylidene groups in the isomeric 2-benzoyl 3 : 4-ethylidene β-methylarabinosides is apparent.

WHEN benzaldehyde and β-methylarabinoside are heated together, syrupy benzylidene β-methylarabinoside is obtained. On standing, the compound partly decomposes to β-methylarabinoside and benzaldehyde. If the conditions used for the condensation are too drastic, dibenzylidene arabinose is also formed. Hydrolysis with 0·25% hydrochloric acid removes the benzylidene residue but not the methyl group, while under identical conditions methylarabinofuranosides are converted into arabinose. This stability of the methyl group (Haworth, *Ber.*, **1928**, **61**, 50) shows that the compound is benzylidene β-methylarabinopyranoside. Methylation of the syrup by Purdie and Irvine's method followed by acid hydrolysis gives a methyl β-methylarabinoside which crystallises as a monohydrate. Removal of the glycosidic group leads to a methyl arabinose from which arabinosazone is obtained with loss of the methyl group. Thus the monomethyl arabinose is **2-*methyl arabinose*** and the benzylidene compound **3 : 4-*benzylidene* β-*methylarabinopyranoside*.** It is interesting to note that the benzylidene group of **3 : 4-*benzylidene* 2-*methyl* β-*methylarabinoside*** is more stable than that of the parent substance. On condensation with acetone, 2-methyl arabinose forms a crystalline product in which C_1 must be unsubstituted as the compound is reducing and methylation followed by hydrolysis regenerates 2-methyl arabinose. The stability of the glycosidic group in the 2-methyl acetone methylarabinosides shows that the substance is pyranosidic and hence the acetone derivative is **2-*methyl* 3 : 4-*acetone arabinose*.**


Mixed 3 : 4-benzylidene β-methylarabinosides
Stable 3 : 4-benzylidene β-methylarabinoside
2-Benzoyl 3 : 4-benzylidene β-methylarabinoside (m. p. 100—102°).
2-Benzoyl 3 : 4-benzylidene β-methylarabinoside (m. p. 126—127°).
A
90% m. p. 97—99°
10% m. p. 120—122°
C
B
B
2-Benzoyl 3 : 4-benzylidene β-methylarabinoside (m. p. 126—127°)
C
2-Benzoyl β-methylarabinoside
B
B
2-Benzoyl 3 : 4-ethylidene β-methylarabinoside (m. p. 141—142°)
2-Benzoyl 3 : 4-ethylidene β-methylarabinoside (m. p. 117°)
Cryst. 3 : 4-ethylidene β-methylarabinoside
Syrupy 3 : 4-ethylidene β-methylarabinoside

A extraction with light petroleum.
B hydrolysis with 0·05N-hydrochloric acid.
C „ „ 0·1N-hydrochloric acid.

Some **3 : 4-benzylidene β-methylarabinoside**, prepared six months previously, after being freed from β-methylarabinoside which had formed, gave on benzoylation **2-*benzoyl* 3 : 4-*benzylidene* β-*methylarabinoside*,** m. p. 126—127°. The benzylidene group of this product is stable to 0·05N-hydrochloric acid. Freshly prepared **3 : 4-benzylidene β-methylarabinoside** on benzoylation yields **2-*benzoyl* 3 : 4-*benzylidene* β-*methylarabinoside*,** m. p. 100—102°. When this is hydrolysed with 0·05N-hydrochloric acid until no further change in optical rotation takes place, the product is **2-*benzoyl* β-*methylarabinoside*** together with the 2-benzoyl 3 : 4-benzylidene β-methylarabinoside, m. p. 126—127°, previously obtained. It is apparent, therefore, that the 2-benzoyl **3 : 4-benzylidene β-methylarabinoside**, m. p. 126—127°, is stable under the conditions of hydrolysis used, while the form, m. p. 100—102°, is a mixture of isomers of which one is benzoyl benzylidene β-methylarabinoside, m. p. 126—127°, and the other is more readily hydrolysed to 2-benzoyl β-methylarabinoside. By repeated extraction with small amounts of light petroleum the mixture (m. p. 100—102°) can be separated into two fractions, (*a*) m. p. 97—99° (90%), and (*b*) m. p. 120—122° (10%). Hydrolysis of (*a*) with 0·05N-hydrochloric acid leads to crystals, m. p. 116—118°, which can be separated by fractional solution into equal parts of 2-benzoyl **3 : 4-benzylidene β-methylarabinoside**, m. p. 126—127°, and 2-benzoyl β-methylarabinoside. Thus (*a*) is a mixture of approximately equal parts of benzoyl benzylidene β-methylarabinoside, m. p. 126—127°, and the less stable isomer. When (*b*) is hydrolysed with 0·05N-hydrochloric acid, a quantitative yield of 2-benzoyl β-methylarabinoside is obtained, showing (*b*) to be the more easily hydrolysed form of 2-benzoyl **3 : 4-benzylidene β-methylarabinoside**. If the concentration of hydrochloric acid used for hydrolysis is increased to 0·1N, then the more stable form of 2-benzoyl **3 : 4-benzylidene β-methylarabinoside** also gives a quantitative yield of 2-benzoyl β-methylarabinoside. The difference in the products obtained by benzoylating freshly prepared and stored specimens of **3 : 4-benzylidene β-methylarabinoside** is due to the fact that

the freshly prepared syrup is a mixture of two isomeric forms—produced because of the asymmetry of the benzylidene group—while in the stored specimen all the more readily hydrolysed form has decomposed, leaving, after purification, only the more stable isomer. The reactions are summarised in the scheme on p. 987.

Paraldehyde and β-methylarabinoside, when shaken with anhydrous copper sulphate and sulphuric acid, yield crystals of ethylidene β-methylarabinoside together with a smaller amount of a syrup of the same analysis. Both compounds give only β-methylarabinoside when hydrolysed with 0·25% hydrochloric acid, and hence both are arabinopyranosides. When the crystals are benzoylated, a *benzoyl ethylidene β-methylarabinoside* (m. p. 141—142°) is obtained, while the syrup gives an *isomer*, m. p. 117°. On acid hydrolysis with 0·05N-hydrochloric acid, both the isomers lead to excellent yields of 2-benzoyl β-methylarabinoside. Thus the crystals and syrup are isomeric forms of 3 : 4-*ethylidene β-methylarabinopyranoside*, the isomerism depending on the new asymmetric centre introduced with the ethylidene group.

Experimental.

Except where otherwise stated, solvents were removed under reduced pressure at $\not>45°$ and benzene and chloroform solutions were dried over anhydrous sodium sulphate. The light petroleum used had b. p. 60—80°.

β-Methyl-l-arabinopyranoside (I).—This method is a modification of that of Hudson (*J. Amer. Chem. Soc.*, 1925, **47**, 267). Finely powdered *l*-arabinose (50 g.) was refluxed for 7 hours with dry methanol (400 ml.) containing hydrogen chloride (1%). The crystals which appeared on cooling were filtered off and washed with dry methanol (3 × 50 ml.). The combined filtrates were refluxed for 2 hours and the solution was concentrated to 150 ml. The crystals obtained were washed with methanol (3 × 30 ml.). The combined crops on recrystallisation from absolute alcohol gave pure (I) (40 g., 73%), m. p. 169—170°, $[\alpha]_D^{18°}$ +244·8° (c = 1·353 in water). Hudson (*loc. cit.*) gives m. p. 169°, $[\alpha]_D^{20°}$ +245·5°.

Benzylidene β-Methylarabinoside.—(i) Under the conditions described by Freudenberg (*Ber.*, 1928, **61**, 1758) for preparing 4 : 6-benzylidene α-methylglucoside no condensation took place, unchanged (I) being recovered. (ii) The method used by Irvine and Scott (*J.*, 1913, **103**, 581) for the glucoside proved to be too drastic, leading to a low yield of impure dibenzylidene arabinose. (iii) Benzaldehyde (50 ml.) and (I) (10 g.) were heated at 140° for 4 hours while a slow stream of carbon dioxide was bubbled through the liquid. Excess of benzaldehyde was removed under reduced pressure and the syrupy product poured into benzene. Unchanged (I) (2 g.) separated (identified by m. p. and mixed m. p.) and was filtered off. After the solution had been washed with 2% sodium hydroxide and dried, the benzene was removed, leaving a pale yellow syrup (10 g.), which was divided into three portions : (*a*) Distillation (160°/0·1 mm.) led to decomposition, crystalline (I) being regenerated. (*b*) After 3 days' exposure to the atmosphere crystals appeared in the syrup, but these were shown to be (I) formed by decomposition. (*c*) Solution of the syrup in hot alcohol followed by careful precipitation with light petroleum yielded a small crop (0·6 g.) of crystals. These were dried, washed with dilute sodium hydroxide and with water, and recrystallised from methanol; m. p. 154° (Found : C, 69·1; H, 5·5; OMe, nil. Dibenzylidene arabinose, $C_{19}H_{18}O_5$, requires C, 69·9; H, 5·5%). [van Ekenstein and Blanksma (*Rec. Trav. chim.*, 1906, **25**, 183) give m. p. 154°.] The residual syrup, freed from solvent, was benzylidene β-methylarabinoside (II), $[\alpha]_D^{18°}$ +112·3° (c = 4·9 in chloroform) (Found : C, 61·7; H, 6·3; OMe, 12·1. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4; OMe, 12·3%). (iv) A purer product was obtained by carrying out the condensation at 135° for 3½ hours with the pressure reduced to 18 ins. of mercury. In this way (I) (10 g.) gave (II) (9·5—10 g.) free from dibenzylidene arabinose, together with unchanged (I) (2·4 g.).

Benzylidene Methyl β-Methylarabinoside.—Two methylations of (II) (9·5 g.) by Purdie and Irvine's method gave a syrup which was dissolved in benzene and extracted with water to remove partially methylated arabinosides which did not contain the benzylidene group. Removal of benzene followed by distillation gave *benzylidene methyl β-methylarabinoside* (III) as a middle fraction (9·5 g., 95%) (Found : C, 63·0; H, 6·7; OMe, 23·0. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·7; OMe, 23·3%).

Methyl β-Methylarabinoside.—(III) (7 g.) was dissolved in acetone (105 ml.) and water (140 ml.), and N/10-hydrochloric acid (105 ml.) was added. After 2 hours' refluxing, the liberated benzaldehyde was extracted with chloroform and the aqueous solution neutralised with barium carbonate. The residue obtained on evaporation to dryness was extracted with chloroform; the resultant solution yielded on concentration a stiff syrup (4 g., 80%) which crystallised immediately. Recrystallisation from ether gave white needles (3·5 g., 68%), m. p. 46—47°, $[\alpha]_D^{18°}$ +208° (c = 2·5 in methyl alcohol). After vacuum drying the crystal form altered and m. p. changed to 63—65°. The change is due to dehydration of *methyl β-methylarabinoside monohydrate* (Found : C, 42·9; H, 8·2; OMe, 31·9. $C_7H_{16}O_6$ requires C, 42·8; H, 8·2; OMe, 31·6%).

Methyl Arabinose.—Hydrolysis of monomethyl β-methylarabinoside with hydrochloric acid gave poor yields owing to the production of furfural derivatives. However, after 3 hours' boiling with 20 parts of sulphuric acid (5%) followed by neutralisation with barium carbonate, filtration, evaporation, and extraction with alcohol, a glass, methyl arabinose (yield 90%), was obtained; $[\alpha]_D^{18°}$ +96·0° (c = 5·0 in water) (Found : OMe, 18·8. $C_6H_{12}O_5$ requires OMe, 18·9%). The product, on treatment with phenylhydrazine, gave arabinosazone (m. p. 149—152°) which did not depress the m. p. of authentic arabinosazone (m. p. 151—153°) (Found : OMe, nil). Thus the compound is 2-*methyl arabinose*.

Condensation of 2-Methyl Arabinose with Acetone.—Monomethyl arabinose (3 g.) was dissolved in acetone (100 ml.) containing hydrogen chloride (0·5%), and after 2 hours the solution was poured into dilute aqueous potassium bicarbonate. Extraction with chloroform gave, on evaporation, a syrup (2·6 g., 68%) which rapidly crystallised. Recrystallisation from aqueous alcohol gave methyl monoacetone arabinose (IV), m. p. 116—118°, $[\alpha]_D^{18°}$ +91·5° in chloroform, +117·5° in acetone, +124·5° in methanol (Found : OMe, 15·6. $C_9H_{16}O_5$ requires OMe, 15·2%).

Examination of (IV).—(i) The crystals reduced Fehling's solution. (ii) Methylation gave a non-reducing syrup, $[\alpha]_D^{18°}$ +124·6° (Found : OMe, 28·0. Methyl acetone methylarabinoside requires OMe, 28·8%). The acetone residue was hydrolysed from this arabinoside with sulphuric acid (0·1%) to give a non-reducing syrupy mixture of methyl methylarabinosides. Thus the acetone condensation product is 2-*methyl* 3 : 4-*monoacetone arabinose*.

Acid Hydrolysis of (II).—The substance (2 g.) was refluxed with hydrochloric acid (50 ml., 0·25%) for 6 hours. The solid, isolated after neutralisation with barium carbonate and removal of the water, was recrystallised from alcohol and identified (m. p., mixed m. p. and $[\alpha]_D$) as β-methylarabinopyranoside (1·4 g., 80%). No arabinose was detected (Fehling's solution) at any stage of the reaction.

Acid Hydrolysis of Methylarabinofuranosides.—The mixed α- and β-methylarabinofuranosides (Baker and Haworth, *J.*, 1925, **127**, 365) when treated as (II) gave arabinose (m. p., mixed m. p.) as the sole product. Thus (II) is 3 : 4-*benzylidene β-methylarabinopyranoside*.

Benzoylation of (II).—A sample of (II prepared six months previously was freed from (I) by shaking its benzene solution with water. Reaction of the purified material (3·8 g.) with benzoyl chloride (2·2 ml.) in pyridine (4 ml.) at room

temperature led, after the usual purification, to a brown syrup (3·8 g.) which on stirring with light petroleum yielded crystals. Recrystallisation from alcohol–light petroleum gave white needles. The syrup obtained by evaporation of the mother liquors yielded, after further treatment with benzoyl chloride, a further crop of crystals. The crops (3·5 g., 67%) which were identical (m. p. and mixed m. p.) were combined and recrystallised from light petroleum to give *2-benzoyl* **3** : **4-*benzylidene β-methylarabinoside***, m. p. 126—127° (V), $[\alpha]_D^{18°}$ +174·0° (*c* = 3·2 in chloroform) (Found : C, 67·1; H, 5·6; OMe, 8·6. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·6; OMe, 8·7%). The experiment was repeated on a larger scale using freshly prepared (II) (27 g.). The alcohol–light petroleum extract of the crude product (34·5 g.) yielded crystals (28·6 g., 75%) which were recrystallised from light petroleum to give *2-benzoyl* **3** : **4-*benzylidene β-methylarabinoside***, m. p. 100—102° (VI), $[\alpha]_D^{18°}$ +214·9° (in chloroform) (Found : C, 67·2; H, 5·6; OMe, 8·6%). The residual syrup (6·9 g.) after retreatment with benzoyl chloride gave crystals (1 g.) identical with (VI) and a second crop (0·2 g.) identical with (V). The non-crystalline residue was impure tribenzoyl β-methylarabinoside (Found : OMe, 6·2. Calc. for $C_{26}H_{24}O_8$: OMe, 6·5%) produced owing to the loss of the benzylidene group during benzoylation.

Examination of (V) *and* (VI).—Hydrochloric acid (1 ml., N/2) was added to a solution of (V) (0·35 g.) in acetone (9 ml.) and the solution boiled for 1 hour. No change in the optical rotation occurred and the product obtained after neutralisation and removal of the solvent proved to be unchanged (V) (m. p. and mixed m. p.).

Under the same conditions (VI) (5 g.) gave a syrup which on rubbing with ether crystallised (2·25 g., 60%); m. p. 137—140°. Recrystallisation from alcohol gave prisms of pure *2-benzoyl β-methylarabinoside* (VII), m. p. 146—147°, $[\alpha]_D^{18°}$ +257° (in acetone) (Found : C, 58·2; H, 6·0; OMe, 11·9. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0; OMe, 11·6%). The alcoholic mother liquors on evaporation yielded (V) (0·2 g.). The ethereal liquors deposited crystals (1 g.) of unchanged (VI) (m. p. and mixed m. p.) and on further concentration a small crop (0·2 g.) of (V) (m. p. and mixed m. p.).

By repeated extraction with small amounts of light petroleum (VI) was separated into three fractions : (*a*) m. p. 97—99°; (*b*) the most soluble, crystallising as agglomerates of prisms, m. p. 120—122°, mixed m. p. with (IV) 94°; and (*c*) intermediate fractions, m. p. 100—102°.

Examination of (VI*a*).—(VI*a*) (10 g.) was hydrolysed under the same conditions as before. After 30 minutes' boiling the acidic reaction mixture was neutralised with barium carbonate and evaporated to dryness. The residue, after extraction with ether, was boiled with acetone. The ether solution gave crystals (3·6 g.) contaminated with benzaldehyde. After being washed with cold light petroleum, the crystals were fractionally extracted with boiling light petroleum to give two fractions (1·5 g.), m. p. 118—121°, and a third, m. p. 115—120°. Recrystallisation of the main fractions from aqueous alcohol gave crystals, m. p. 126—127°, shown to be identical with (V) (m. p. and mixed m. p.) (Found : OMe, 8·9%).

The acetone solution gave crystals (5·6 g.) which on recrystallisation from alcohol deposited a main crop (3·4 g.), m. p. 116—117°, and a small second crop, m. p. 108°. A further recrystallisation of the main crop did not alter the m. p., yet analysis (Found : OMe, 10·1%) showed that complete removal of the benzylidene group had not been achieved. The crystals (2·4 g.) were extracted twice with small amounts of alcohol to give two fractions, of which the first (m. p. 116—120°) was further extracted with boiling light petroleum to give a soluble fraction (1 g.), m. p. 125—126°, shown (m. p. and mixed m. p.) to be (V), and an insoluble fraction (0·1 g.) identical with the crop obtained from the second alcohol extraction. These crystals were combined and recrystallised from ether–alcohol to give colourless prisms, m. p. 146—147°, shown to be (VII) (m. p., mixed m. p., and $[\alpha]_D$). Thus (VI*a*) is a mixture of approximately equal quantities of (IV) and a more readily hydrolysed isomer which gives (VII) on hydrolysis.

Examination of (VI*b*).—(VI*b*) (2·1 g.) was hydrolysed as for (VI) to give crystals (yield 98%), m. p. 143—146°. Recrystallisation gave pure (VII) (m. p. and mixed m. p.). No other product was isolated. Thus, (VI*b*) is a pure isomer of (V), and (VI) is a mixture of (VI*b*) and (V).

Hydrolysis of (V).—(V) (1 g.) was refluxed in a solution of acetone (17 ml.) containing hydrochloric acid (3 ml., 0·67N) for 2 hours. No hydrolysed material was detected and pure (VII) (m. p. and mixed m. p.) was isolated.

Ethylidene β-Methylarabinoside.—Anhydrous copper sulphate (5 g.) and (I) (5 g.) were shaken for 1 day at room temperature with dry, neutralised paraldehyde (50 ml.) containing concentrated sulphuric acid (0·5 ml.). The filtered solution was neutralised with potassium carbonate and a syrupy product (4·5 g.) isolated after filtration and evaporation. The bulk of the syrup dissolved in boiling light petroleum, but a small amount (0·7 g.) of unchanged (I) remained undissolved. The solution, on cooling, deposited sticky crystals. After tiling and recrystallising from light petroleum, ethylidene β-methylarabinoside (VIII) (3·5 g., 58%) was obtained, m. p. 76°, $[\alpha]_D^{18°}$ +204·6° (*c* = 3·6 in chloroform) (Found : C, 50·5; H, 7·5; OMe, 16·2. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 16·3%). After exposure to the laboratory atmosphere for 14 days some decomposition to (I) and acetaldehyde had taken place, but when the material was stored in a sealed tube it was indefinitely stable. Extraction of the tile with boiling light petroleum gave a colourless syrup (IX) (1·2 g., 20%) (Found : OMe, 16·2%). Its stability is identical with that of (VIII).

Examination of (VIII) *and* (IX).—(i) *Acid hydrolysis.* Under the conditions described for (II) the sole product in each case was (I) uncontaminated by any reducing component.

(ii) *Benzoylation.* Treatment with benzoyl chloride (25% excess) in pyridine at room temperature gave almost quantitative yields of the monobenzoyl derivatives which were recrystallised from aqueous alcohol. (VIII) gave benzoyl ethylidene β-methylarabinoside, m. p. 141—142° (X), $[\alpha]_D^{20°}$ +125° (*c* = 2·6 in chloroform) (Found : C, 54·2; H, 5·4; OMe, 10·5. $C_{15}H_{18}O_6$ requires C, 54·3; H, 5·5; OMe, 10·5%). (IX) gave benzoyl ethylidene β-methylarabinoside, m. p. 117° (XI), $[\alpha]_D^{20°}$ +109° (*c* = 3·1 in chloroform) (Found : C, 54·3; H, 5·4; OMe, 10·5%).

Acid Hydrolysis of (X) *and* (XI).—Each substance was hydrolysed separately under the conditions described for (VI*b*). The products, which were identical, proved to be (VII) (m. p. and mixed m. p.).

Thus, (VIII) and (IX) are isomeric forms of **3** : **4-*ethylidene β-methylarabinopyranoside*** and (X) and (XI) the corresponding ***2-benzoyl*** derivatives.

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212. *Reactions of β-Methylarabinoside. Part II. 3 : 4-Acetone β-Methylarabinopyranoside. 3 : 4-Dimethyl Arabinose. The Conversion of Arabinose into Xylose.*

By JOHN HONEYMAN.

In the presence of a dehydrating agent, acetone condenses with β-methyl-*l*-arabinoside to yield liquid 3 : 4-*acetone β-methylarabinopyranoside*. This has been used as the starting material to prepare 3 : 4-*dimethyl arabinose* and also 3 : 4-*ditosyl* 2-*acetyl β-methylarabinoside* and 2-*tosyl* 3 : 4-*diacetyl β-methylarabinoside*. Alkaline hydrolysis leads, respectively, to 2 : 3-*anhydro β-methyl*-l-*lyxoside* and 2 : 3-*anhydro β-methyl*-l-*riboside* both of which yield, on further alkaline hydrolysis, β-methyl-*l*-arabinoside plus *β-methyl*-l-*xyloside*.

β-METHYLARABINOSIDE reacts with acetone in the presence of a dehydrating agent to form monoacetone β-methylarabinoside, the reaction being rapid and the yield good when phosphoric oxide is used. The product, after distillation, is a colourless liquid, the stability of which is similar to that of 3 : 4-ethylidene β-methylarabinoside (Part I). Benzoylation in the usual manner leads to a complex reaction which involves loss of the glycosidic methyl group, but under mild conditions an almost theoretical yield of a crystalline benzoate is obtained. Hydrolysis with 0·36% hydrochloric acid removes only the acetone residue to yield 2-benzoyl β-methylarabinoside (see Part I). The stability of the glycosidic group shows that the acetone compound is pyranosidic, and the formation of 2-benzoyl β-methylarabinoside proves that C_2 is unsubstituted. The high yield obtained on benzoylation shows that the liquid is a pure compound and not an azeotropic mixture of isomers. Hence the acetone derivative is 3 : 4-*acetone β-methylarabinopyranoside* and the benzoate is 2-*benzoyl* 3 : 4-*acetone β-methylarabinoside*. Thus when benzaldehyde, acetaldehyde, or acetone reacts with β-methylarabinoside the hydroxyls on C_3 and C_4 are involved. Further proof of the constitution of 3 : 4-acetone β-methylarabinoside is obtained by methylation and subjecting the monomethyl derivative (*i.e.*, 2-*methyl* 3 : 4-*acetone β-methylarabinoside*) to partial hydrolysis. The product so obtained is 2-methyl β-methylarabinoside crystallising as the monohydrate (identical with that described in Part I).

Methylation of 2-benzoyl β-methylarabinoside leads to 2-*benzoyl* 3 : 4-*dimethyl β-methylarabinoside* as a syrup which gives, on alkaline hydrolysis, 3 : 4-*dimethyl β-methylarabinoside* as a colourless liquid. From this 3 : 4-*dimethyl arabinose* is obtained, also as a liquid, by acid hydrolysis. The composition of 3 : 4-dimethyl β-methylarabinoside can be verified by treatment with tosyl chloride, which gives an excellent yield of crystalline 2-*tosyl* 3 : 4-*dimethyl β-methylarabinoside*. This compound, prepared also by an alternative route (see below), proves that no migration took place during the methylation of 2-benzoyl β-methylarabinoside.

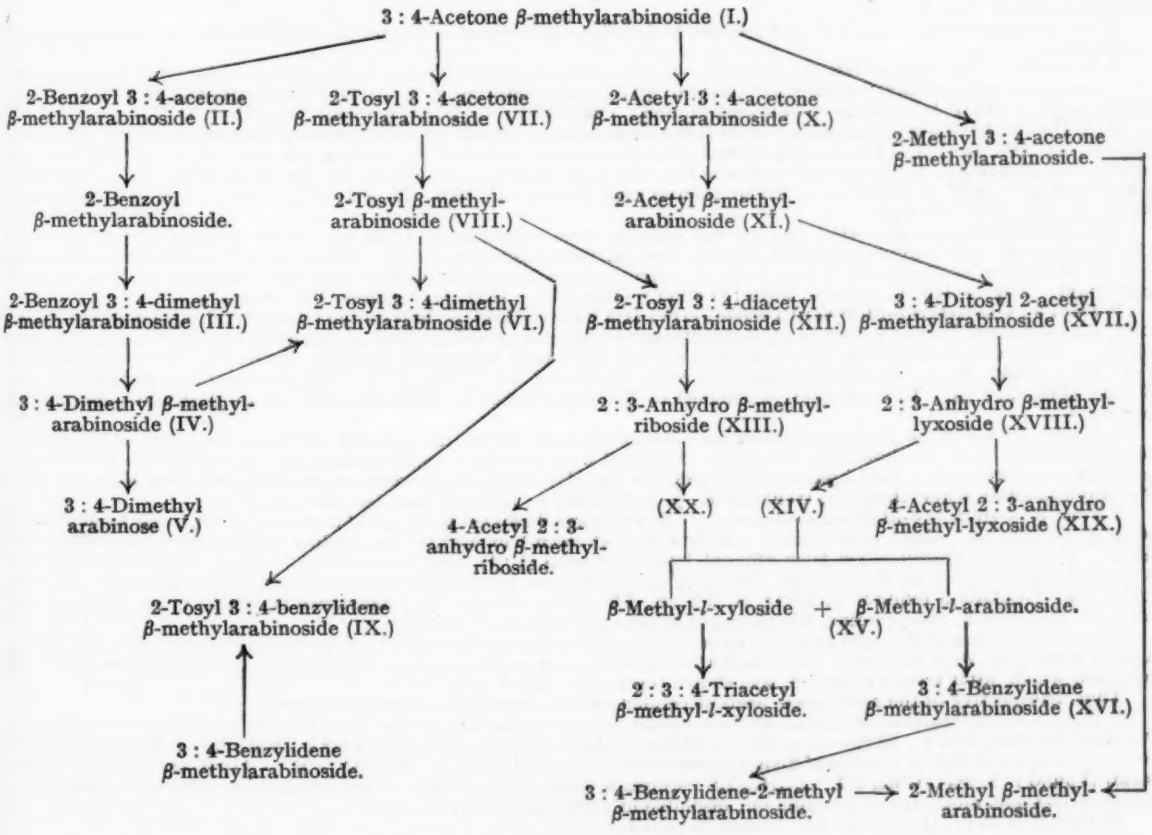
Reaction of 3 : 4-acetone β-methylarabinoside with tosyl chloride in pyridine leads to 2-*tosyl* 3 : 4-*acetone β-methylarabinoside* from which the acetone residue can be removed with acid to provide crystalline 2-*tosyl β-methylarabinoside*. It is to be noted that the stability of the acetone residue is greatly increased when C_2 carries a substituent other than the hydroxyl group. When 2-tosyl β-methylarabinoside is methylated the crystalline product obtained is 2-tosyl 3 : 4-dimethyl β-methylarabinoside identical with the compound already prepared. Condensation with benzaldehyde also yields a crystalline derivative which is 2-*tosyl* 3 : 4-*benzylidene β-methylarabinoside*. When freshly prepared 3 : 4-benzylidene β-methylarabinoside is treated with tosyl chloride a poor yield (25%) of the identical 2-tosyl 3 : 4-benzylidene β-methylarabinoside is obtained together with a larger amount of a syrup with the composition of an impure tritosyl β-methylarabinoside. It appears, therefore, that the slowness of the tosylation reaction results in only the more stable benzylidene β-methylarabinoside being substituted, the less stable form decomposing and yielding tritosyl β-methylarabinoside. Also, when 2-tosyl β-methylarabinoside condenses with benzaldehyde only the more stable 2-tosyl 3 : 4-benzylidene β-methylarabinoside is produced. The benzylidene group of this compound is unusually stable, resisting hydrolysis with 0·45% hydrochloric acid. In fact, no method was found to eliminate the benzaldehyde residue without simultaneously removing the glycosidic methyl group.

The crystalline 3 : 4-ethylidene β-methylarabinoside (see Part I) gives a high yield of 2-*tosyl* 3 : 4-*ethylidene β-methylarabinoside* from which the ethylidene group is readily removed leading to 2-tosyl β-methylarabinoside. However, the simplest method of preparing 2-tosyl β-methylarabinoside is through the acetone compound.

On acetylation of 2-tosyl β-methylarabinoside, crystalline 2-*tosyl* 3 : 4-*diacetyl β-methylarabinoside* is obtained in excellent yield. Mild alkaline hydrolysis produces a syrup with the analysis of an anhydro methylpentoside which forms a crystalline monoacetate in good yield. By analogy with similar reactions on hexoses (for a review see Peat, *Ann. Reports*, 1939, **36**, 259), it is thought that the tosyl group is removed with Walden inversion on C_2 accompanied by formation of an anhydro group between C_2 and C_3. The yield of crystalline monoacetate is noteworthy since it points to the syrup being one substance only, which is considered to be 2 : 3-*anhydro β-methyl*-l-*riboside* and hence the acetyl derivative is 4-*acetyl* 2 : 3-*anhydro β-methylriboside*. Further alkaline hydrolysis opens the anhydro ring to give a syrup with the composition of a methylpentoside. Treatment of this with benzaldehyde followed by addition of the syrupy product to benzene gives a precipitate of crystals with physical constants corresponding to *β-methyl*-l-*xyloside* [Fischer (*Ber.*, 1895, **28**, 1157) and Dale (*J. Amer. Chem. Soc.*, 1915, **37**, 2747) have prepared the corresponding *d*-xyloside] which on acetylation gives 2 : 3 : 4-*triacetyl β-methyl*-l-*xyloside*. [Hudson and Dale (*J. Amer. Chem. Soc.*, 1918, **40**, 1000) have prepared the *d*-compound.] The benzene solution yields a syrupy benzylidene methylpentoside which by methylation and hydrolysis gives 2-methyl β-methylarabinoside. Hence the syrupy methylpentoside obtained on ring scission must be a mixture of β-methyl-*l*-xyloside and β-methyl-*l*-arabinoside. It is known that β-methyl-

xyloside does not react with benzaldehyde under the conditions used (Robertson and Speedie, *J.*, 1934, 824). The yields point to there being about 75% of the former and 25% of the latter. These products are obtained from the 2 : 3-anhydro compound by opening the ethylene oxide ring at the two possible points accompanied in each case by Walden inversion. No trace could be found of a riboside which would be formed if the ring were opened without inversion. Since only the two products named are obtained, the 2 : 3-anhydro ring is the only one formed. This is striking proof of the great ease with which an ethylene oxide ring can be produced, since a 2 : 4-anhydro ring is also possible.

2-Acetyl 3 : 4-acetone β-methylarabinoside, prepared by acetylating 3 : 4-acetone β-methylarabinoside, leads on acid hydrolysis to *2-acetyl β-methylarabinoside*, which can be tosylated to *3 : 4-ditosyl 2-acetyl β-methylarabinoside*. Alkaline hydrolysis of this gives a syrupy anhydro methylpentoside which yields a crystalline monoacetate distinct from 4-acetyl 2 : 3-anhydro β-methylriboside. The syrupy anhydro compound is considered to be *2 : 3-anhydro β-methyl-l-lyxoside*, and its crystalline acetate *4-acetyl 2 : 3-anhydro β-methyl-l-lyxoside*. In this case further hydrolysis with alkali leads to a mixture of methylpentosides proved, in the same way as before, to consist of about 65% of β-methyl-*l*-xyloside and 35% of β-methyl-*l*-arabinoside. This is further proof that only the 2 : 3-anhydro ring is formed, that no 2 : 4-anhydro compound is present, and that no 3 : 4-anhydro ring is formed, *i.e.*, that elimination of *cis*-tosyl groups on adjacent carbons is not accompanied by anhydro ring formation.


3 : 4-Acetone β-methylarabinoside (I.)
2-Benzoyl 3 : 4-acetone β-methylarabinoside (II.)
2-Tosyl 3 : 4-acetone β-methylarabinoside (VII.)
2-Acetyl 3 : 4-acetone β-methylarabinoside (X.)
2-Methyl 3 : 4-acetone β-methylarabinoside.
2-Benzoyl β-methylarabinoside.
2-Tosyl β-methylarabinoside (VIII.)
2-Acetyl β-methylarabinoside (XI.)
2-Benzoyl 3 : 4-dimethyl β-methylarabinoside (III.)
2-Tosyl 3 : 4-dimethyl β-methylarabinoside (VI.)
2-Tosyl 3 : 4-diacetyl β-methylarabinoside (XII.)
3 : 4-Ditosyl 2-acetyl β-methylarabinoside (XVII.)
3 : 4-Dimethyl β-methylarabinoside (IV.)
2 : 3-Anhydro β-methylriboside (XIII.)
2 : 3-Anhydro β-methyllyxoside (XVIII.)
3 : 4-Dimethyl arabinose (V.)
(XX.)
(XIV.)
4-Acetyl 2 : 3-anhydro β-methyl-lyxoside (XIX.)
4-Acetyl 2 : 3-anhydro β-methylriboside.
2-Tosyl 3 : 4-benzylidene β-methylarabinoside (IX.)
β-Methyl-l-xyloside + β-Methyl-l-arabinoside. (XV.)
2 : 3 : 4-Triacetyl β-methyl-l-xyloside.
3 : 4-Benzylidene β-methylarabinoside (XVI.)
3 : 4-Benzylidene β-methylarabinoside.
3 : 4-Benzylidene-2-methyl β-methylarabinoside.
2-Methyl β-methylarabinoside.

Experimental.

Except where otherwise stated, solvents were removed under reduced pressure at $>45°$ and benzene and chloroform solutions were dried over anhydrous sodium sulphate. The light petroleum used had b. p. 60—80°.

l-*Arabinose*.—This was prepared by the acid hydrolysis of mesquite gum (*Org. Synth.*, Coll. Vol. I, p. 60).

Acetone β-Methylarabinoside.—β-Methylarabinoside (for preparation see Part I) condensed with acetone in the presence of zinc chloride, hydrogen chloride, sulphuric acid, anhydrous copper sulphate, or phosphoric oxide. The best yield was obtained using phosphoric oxide, and this was used in the standard method of preparation.

Excess of phosphoric oxide (10 g.) was added with vigorous agitation to a suspension of β-methylarabinoside (5 g.) in acetone (300 ml.). After being shaken for 5 minutes at room temperature the acetone solution was decanted and the inorganic residue washed with acetone (3 × 20 ml.). The combined extracts were neutralised with solid potassium carbonate. Filtration followed by distillation of the solvent left a pale yellow, slightly reducing syrup (5 g.) contaminated by a trace of acetone auto-condensation products. Distillation gave colourless, non-reducing, liquid acetone β-methylarabinoside (I) (11 g., 63%), b. p. 82°/0·1 mm., $[\alpha]_D^{20°}$ + 199·1° (c = 3·3 in chloroform) (Found: C, 52·2; H, 7·8; OMe, 15·1. $C_9H_{16}O_5$ requires C, 52·5; H, 7·8; OMe, 15·2%), soluble in water and most organic solvents except aliphatic hydrocarbons. Its stability was similar to that of 3 : 4-ethylidene β-methylarabinoside.

Benzoyl Acetone β-Methylarabinoside.—(i) (I) (0·5 g.) was dissolved in pyridine (10 ml.), and benzoyl chloride (0·5 g., 50% excess) added. After 12 hours at room temperature, the reaction mixture was poured into a large volume of water and the product extracted with chloroform, and the solution washed with 2% sulphuric acid, 2% potassium bicarbonate solution, and dried. Removal of the solvent left a mobile syrup (0·6 g.) which had a strong smell of methyl benzoate. The syrup reduced Fehling's solution confirming that loss of methoxyl group had taken place.

(ii) The above experiment was repeated under milder conditions. (I) (0·5 g.) was dissolved in pyridine (5 ml.) and to this was added a solution of benzoyl chloride (0·5 g.) in pyridine (5 ml.). The temperature was maintained at −5° for 12 hours, and the product isolated as before. A reducing syrup was again obtained (Found: OMe, 4·7. $C_{16}H_{20}O_6$ requires OMe, 10·0%).

(iii) (I) (0·5 g.) was dissolved in pyridine (5 ml.) and cooled to −5°. A solution of the theoretical quantity of benzoyl chloride (0·35 g.) in pyridine (5 ml.) was slowly dropped into this with efficient agitation. This operation took 35 minutes. After a further 5 minutes at −5° the solution was poured on crushed ice. The product, purified as before, was obtained in theoretical yield as non-reducing crystals. Recrystallisation was difficult as the substance was extremely soluble in all the common solvents except water. The solvent ultimately used was ethanol–water (10 : 90) at $\gtrsim$60°. Five recrystallisations gave pure benzoyl acetone β-methylarabinoside (II), m. p. 78—79°, $[\alpha]_D^{18°}$ + 206·7° (*c* = 1·3 in chloroform) (Found: C, 61·8; H, 6·4; OMe, 10·0. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5; OMe, 10·0%).

Benzoyl β-Methylarabinoside.—(II) (0·45 g.) was dissolved in methanol (24·5 ml.) and hydrochloric acid (0·5 ml., 5N) added. Polarimetric observation showed that no reaction took place at room temperature. The solution was therefore refluxed until the rotation was constant (10 hours). After neutralising with silver carbonate, the solution was filtered and the solvent removed. The residue was dissolved in chloroform and dried. Evaporation yielded a non-reducing syrup (0·4 g.) which crystallised on stirring. Recrystallisation from ethanol–light petroleum gave pure 2-benzoyl β-methylarabinoside, m. p. 147° (Found: OMe, 11·5. Calc. for $C_{13}H_{16}O_6$: OMe, 11·6%), identical (m. p. and mixed m. p.) with that prepared in Part I.

These experiments show that (I) is 3 : 4-*acetone β-methylarabinopyranoside*, and (II) is 2-*benzoyl* 3 : 4-*acetone β-methylarabinoside*.

2-*Benzoyl* 3 : 4-*Dimethyl β-Methylarabinoside.*—Complete methylation of 2-benzoyl β-methylarabinoside (2·4 g.) required five treatments with methyl iodide–silver oxide to give syrupy 2-*benzoyl* 3 : 4-*dimethyl β-methylarabinoside* (III) (2·2 g., 83%), $[\alpha]_D^{18°}$ + 143·5° (*c* = 2·6 in chloroform) (Found: OMe, 30·9. $C_{15}H_{20}O_6$ requires OMe, 31·4%).

3 : 4-*Dimethyl β-Methylarabinoside.*—(III) (1·9 g.) was refluxed for one hour in a solution of aqueous sodium hydroxide (10 ml., 2N) and alcohol (10 ml.). Extraction with chloroform, followed by evaporation, gave 3 : 4-*dimethyl β-methylarabinoside* (IV) (1·1 g., 89%) as a pale yellow syrup, which distilled uniformly (b. p. 83—84°/0·1 mm.) to yield a colourless liquid (1·0 g.); $[\alpha]_D^{18°}$ + 210·6° (*c* = 3·8 in chloroform) (Found: C, 49·6; H, 8·3; OMe, 48·6. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3; OMe, 48·4%).

3 : 4-*Dimethyl Arabinose.*—(IV) (2·5 g.) was refluxed with sulphuric acid (50 ml., N) for 4 hours and the solution then neutralised with barium carbonate, filtered through silica, and evaporated. Purification by chloroform extraction gave 3 : 4-*dimethyl arabinose* (V) (2·1 g., 91%) as a syrup, which distilled uniformly (b. p. 123—124°/0·1 mm.) to a colourless liquid; $[\alpha]_D^{18°}$ + 116° (*c* = 4·2 in water) (Found: OMe, 34·7. $C_7H_{14}O_5$ requires OMe, 34·8%).

2-*Tosyl* 3 : 4-*Dimethyl β-Methylarabinoside.*—(IV) (1·3 g.) was dissolved in pyridine (10 ml.) and tosyl chloride (1·7 g., 25% excess) added. After 4 days at room temperature the product was isolated in the usual way as a hard crystalline mass. A single recrystallisation from aqueous alcohol gave pure needles of 2-*tosyl* 3 : 4-*dimethyl β-methylarabinoside* (VI) (2·2 g., 94%), m. p. 111—112° (Found: C, 51·5; H, 6·4; S, 9·1; OMe, 26·5. $C_{15}H_{22}O_7S$ requires C, 52·0; H, 6·4; S, 9·2; OMe, 26·8%). The constitution assigned to (VI) was verified by its preparation by an alternative method (see below).

2-*Methyl* 3 : 4-*Acetone β-Methylarabinoside.*—Methylation of (I) by the method of Purdie and Irvine gave, after recrystallisation from alcohol–light petroleum, 2-methyl 3 : 4-acetone β-methylarabinoside, m. p. 62°, $[\alpha]_D^{20°}$ + 162·5° (*c* = 4·6 in chloroform). Acid hydrolysis [as descibed for (II)] followed by recrystallisation from ether gave 2-methyl β-methylarabinoside monohydrate, identical (m. p. and mixed m. p.) with that described in Part I.

2-*Tosyl* 3 : 4-*Acetone β-Methylarabinoside.*—(I) (0·58 g.) was dissolved in excess of pyridine (10 ml.), and tosyl chloride (0·86 g., 50% excess) added with cooling. After 4 days at room temperature the product (0·97 g., 93%) was isolated as usual. A single recrystallisation from ethanol–light petroleum (1 : 1) gave pure needles (0·83 g., 80%) of 2-*tosyl* 3 : 4-*acetone β-methylarabinoside* (VII), m. p. 136°, $[\alpha]_D^{19°}$ + 181·3° (*c* = 1·68 in chloroform) (Found: C, 53·5; H, 6·1; S, 8·7; OMe, 8·9. $C_{16}H_{22}O_7S$ requires C, 53·6; H, 6·1; S, 8·9; OMe, 8·7%). The substance is soluble in alcohol, acetone, benzene, chloroform, and pyridine, but insoluble in light petroleum and water.

The syrups obtained from the reactions of acetone with β-methylarabinoside in the presence of the various condensing agents mentioned were subjected individually to reaction with tosyl chloride. In each case a crystalline product was obtained which, after recrystallisation, was shown (m. p. and mixed m. p.) to be (VII).

Thus, irrespective of the agent used, acetone condenses with β-methylarabinoside to give (I).

2-*Tosyl β-Methylarabinoside.*—(VII) (0·5 g.) was hydrolysed as for (II) except that 8 hours' refluxing was necessary. A colourless glass (0·4 g., 88%) was obtained which crystallised after being stored for several years. Recrystallisation from aqueous alcohol gave needles of 2-*tosyl β-methylarabinoside* (VIII), m. p. 48—49°, $[\alpha]_D^{18°}$ + 110·9° (*c* = 1·14 in chloroform) (Found: S, 9·9; OMe, 9·7. $C_{13}H_{18}O_7S$ requires S, 10·6; OMe, 9·8%). The substance is soluble in chloroform, benzene, acetone, alcohol, and pyridine but insoluble in water and light petroleum.

Methylation of (VIII) (Purdie and Irvine) gave (VI).

Condensation of (VIII) with benzaldehyde, under the conditions described for the preparation of 3 : 4-benzylidene β-methylarabinoside in Part I, gave (IX) (identified by m. p. and mixed m. p.).

2-*Tosyl* 3 : 4-*Benzylidene β-Methylarabinoside.*—Since 3 : 4-benzylidene β-methylarabinoside (Part I) decomposed readily it was subjected as soon as isolated to treatment with tosyl chloride.

3 : 4-Benzylidene β-methylarabinoside (5 g.) was dissolved in pyridine and tosyl chloride (6·5 g.) added. After 4 days at room temperature the product was obtained in the usual manner as a light brown syrup. After being rubbed with a rod this yielded a hard, crystalline mass contaminated with syrup. The crystals were less soluble in hot alcohol than the syrup, which was removed by repeated treatment with this solvent. The crystals were tiled and recrystallised from absolute ethanol–light petroleum to give needles (2 g., 25%) of 2-*tosyl* 3 : 4-*benzylidene β-methylarabinoside* (IX), m. p. 144—145°, $[\alpha]_D^{18°}$ + 188·0° (*c* = 1·26 in benzene) (Found: C, 59·0; H, 5·4; S, 7·8; OMe, 7·5. $C_{20}H_{22}O_7S$ requires C, 59·1; H, 5·4; S, 7·9; OMe, 7·6%).

The syrup (4 g.) obtained was subjected to a further treatment with tosyl chloride but no further condensation took place. Analysis of the syrup showed it to be impure tritosyl β-methylarabinoside (Found: C, 51·2; H, 4·7; OMe, 4·3. Calc. for $C_{27}H_{30}O_{11}S$: C, 51·7; H, 4·8; OMe, 4·9%).

Acid Hydrolysis of 2-*Tosyl* 3 : 4-*Benzylidene β-Methylarabinoside.*—Prolonged boiling with methanolic hydrochloric acid in concentrations up to 0·45% led to no hydrolysis. More concentrated acid removed the glycosidic methyl as well as the benzylidene group.

2-Tosyl 3 : 4-Ethylidene β-Methylarabinoside.—Crystalline ethylidene β-methylarabinoside (Part I) (0·35 g.) was dissolved in pyridine (10 ml.) containing tosyl chloride (0·5 g., 50% excess). After 30 minutes at room temperature the product was isolated in the usual way to give crude crystals (0·65 g.) which when recrystallised from ethanol–light petroleum (50 : 50) yielded colourless plates of *2-tosyl 3 : 4-ethylidene β-methylarabinoside* (0·55 g., 86%), m. p. 134—135°, $[\alpha]_D^{19°}$ + 188·4° (*c* = 1·8 in chloroform) (Found: C, 52·0; H, 5·9; S, 9·1; OMe, 8·9. $C_{15}H_{20}O_7S$ requires C, 52·3; H, 5·8; S, 9·3; OMe, 9·0%).

Hydrolysis as described for (II), except that 1 hour's refluxing was sufficient, gave (VIII) (m. p. and mixed m. p.).

2-Tosyl 3 : 4-Diacetyl β-Methylarabinoside.—(VIII) (0·35 g.) was dissolved in pyridine (5 ml.) containing acetic anhydride (0·35 g., 50% excess) and left at room temperature for 12 hours. The product (0·44 g., 98%) gave on recrystallisation from ethanol–light petroleum (15 : 85) pure *2-tosyl 3 : 4-diacetyl β-methylarabinoside* (XII) (0·35 g.) as colourless prisms, m. p. 116°, $[\alpha]_D^{19°}$ +122·5° (*c* = 2·0 in chloroform) (Found: S, 8·0; OMe, 7·6. $C_{17}H_{22}O_9S$ requires S, 8·0; OMe, 7·7%). The crystals are soluble in all common solvents except water and light petroleum.

Alkaline Hydrolysis of 2-Tosyl 3 : 4-Diacetyl β-Methylarabinoside.—(XII) (5 g.) was added to methanol (100 ml.) containing sodium (2 g.) and the solution kept at room temperature for 48 hours. After careful neutralisation with acetic acid and dilution with water, the product was extracted with chloroform and isolated as a pale yellow syrup (1·6 g., 90%) with the composition of an anhydro methylpentoside, $[\alpha]_D^{18°}$ + 36·8° (*c* = 2·0 in chloroform) (Found: C, 49·0; H, 6·8; OMe, 21·1. $C_6H_{10}O_4$ requires C, 49·3; H, 6·8; OMe, 21·2%). By analogy with similar reactions on hexosides this is considered to be *2 : 3-anhydro β-methylriboside* (XIII).

Acetylation of (XIII) (0·5 g.) with acetic anhydride in pyridine led to a crystalline product which on recrystallisation from aqueous alcohol gave needles (0·5 g., 78%) of *4-acetyl 2 : 3-anhydro β-methylriboside*, m. p. 82—83°, $[\alpha]_D^{18}$ + 73·6° (*c* = 3·5 in chloroform) (Found: OMe, 16·3. $C_8H_{12}O_5$ requires OMe, 16·5%). No other substance was isolated.

Alkaline Hydrolysis of 2 : 3-Anhydro β-Methylriboside.—(XIII) (4·1 g.) was heated on a boiling water-bath for 48 hours with aqueous sodium hydroxide (250 ml., 5%). After neutralisation with acetic acid the solution was taken to dryness and the organic matter dissolved in absolute alcohol. Removal of the solvent gave a pale yellow syrup (4 g., 90%) having the composition of a methylpentoside (XIV), $[\alpha]_D^{18°}$ + 106·8° (*c* = 2·3 in water) (Found: C, 44·2; H, 7·4; OMe, 18·7. $C_6H_{12}O_5$ requires C, 43·9; H, 7·3; OMe, 18·9%).

Examination of (XIV).—The syrup (3·2 g.) was treated with benzaldehyde under the conditions described for the preparation of 3 : 4-benzylidene β-methylarabinoside (Part I). On pouring the product into benzene, crystals (XV) (2·3 g.) of a methylpentoside (Found: OMe, 18·8. $C_6H_{12}O_5$ requires OMe, 18·9%) were precipitated; these were filtered off. Evaporation of benzene left a syrup (XVI) (1·2 g.) with the composition of a benzylidene methylpentoside (Found: OMe, 12·4. $C_{13}H_{16}O_5$ requires OMe, 12·3%).

Examination of (XV).—The crystals after recrystallisation from alcohol had m. p. 155—156°, $[\alpha]_D^{18°}$ + 62·5° (*c* = 2·4 in water) and mixed m. p. with β-methylarabinoside (m. p. 169—170°) 130—135°. From the fact that the substance did not condense with benzaldehyde, and from the physical constants, the crystals were thought to be *β-methyl-l-xylopyranoside*. For β-methyl-*d*-xylopyranoside Fischer (*loc. cit.*) gives m. p. 156—157°, $[\alpha]_D$ − 65·8° (*c* = 9 in water), and Dale (*loc. cit.*) gives m. p. 155—156°, $[\alpha]_D^{20°}$ − 65·3°.

Acetylation of (XV) with acetic anhydride–sodium acetate gave *2 : 3 : 4-triacetyl β-methyl-l-xyloside* which after recrystallisation from water had m. p. 115—116°, $[\alpha]_D^{18°}$ + 59·9° (*c* = 2·3 in chloroform) (Found: OMe, 10·6. $C_{13}H_{18}O_8$ requires OMe, 10·7%). Hudson and Dale (*loc. cit.*) give, for triacetyl β-methyl-*d*-xyloside, m. p. 115°, $[\alpha]_D^{20°}$ − 60·8° (*c* = 2·7 in chloroform). This verifies that (XV) is β-methyl-*l*-xyloside.

Examination of (XVI).—Methylation followed by acid hydrolysis (as described for the preparation of 2-methyl β-methylarabinoside in Part I) gave 2-methyl β-methylarabinoside monohydrate identified by m. p. and mixed m. p. (46—47°) with an authentic specimen.

Thus (XVI) is *3 : 4-benzylidene β-methylarabinoside* and (XIV) is a mixture of approximately 75% of β-methyl-*l*-xyloside and 25% of β-methyl-*l*-arabinoside.

2-Acetyl 3 : 4-Acetone β-Methylarabinoside.—Acetic anhydride (0·38 g., 50% excess) was added to (I) (0·5 g.) in pyridine (5 ml.). After 2 hours the reaction mixture was flooded with saturated potassium chloride solution and the product extracted with chloroform. This solution was purified by shaking with 2% hydrochloric acid saturated with potassium chloride followed by saturated potassium carbonate solution, and dried. The chloroform was evaporated leaving almost the theoretical amount of crystalline product. Since the crystals were soluble in all the common solvents, including water, purification was difficult. However, recrystallisation from a small amount of boiling water, followed by a further recrystallisation from light petroleum, gave pure *2-acetyl 3 : 4-acetone β-methylarabinoside* (X), m. p. 76—77°, $[\alpha]_D^{16°}$ + 123·6° (*c* = 1·2 in water) (Found: OMe, 12·4. $C_{11}H_{18}O_6$ requires OMe, 12·6%).

2-Acetyl β-Methylarabinoside.—Hydrolysis of (X) as for (VII) gave, on recrystallisation from ethanol–light petroleum, colourless prisms of *2-acetyl β-methylarabinoside* (XI), m. p. 172°, $[\alpha]_D^{16°}$ + 252·2° (*c* = 1 in water) (Found: OMe, 15·1. $C_8H_{14}O_6$ requires OMe, 15·0%).

3 : 4-Ditosyl 2-Acetyl β-Methylarabinoside.—Treatment of (X) (0·4 g.) in pyridine with tosyl chloride (1 g., 25% excess) at room temperature for 4 days followed by the usual purification gave, after recrystallisation from ethanol–light petroleum, prisms (0·8 g., 80%) of *3 : 4-ditosyl 2-acetyl β-methylarabinoside* (XVII), m. p. 62—63°, $[\alpha]_D^{18°}$ + 173·2° (*c* = 3·3 in chloroform) (Found: S, 12·4; OMe, 6·0. $C_{32}H_{36}O_{10}S_2$ requires S, 12·5; OMe, 6·0%).

Alkaline Hydrolysis of 3 : 4-Ditosyl 2-Acetyl β-Methylarabinoside.—This was carried out as for (XII). A similar yield was obtained of a syrupy *anhydro methylpentoside* (XVIII); $[\alpha]_D^{18°}$ + 127·6° (*c* = 1·3 in chloroform) (Found: C, 49·5; H, 6·8; OMe, 21·3. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9; OMe, 21·2%).

Acetylation of (XVIII) showed it to be distinct from (XIII) since the crystalline product, considered to be *4-acetyl 2 : 3-anhydro β-methyl-lyxoside* (XIX), had m. p. 112—114°, $[\alpha]_D^{18°}$ + 106·9° (*c* = 2·8 in chloroform) (Found: OMe, 16·6. $C_8H_{12}O_5$ requires OMe, 16·5%).

Alkaline Hydrolysis of 4-Acetyl 2 : 3-Anhydro β-Methyl-lyxoside.—When treated as described for (XIII), a pale yellow syrup (XX) (88% yield) was obtained; $[\alpha]_D^{18°}$ + 108·5° (*c* = 2·5 in water). Its composition was that of a methyl pentoside (Found: OMe, 18·8. Calc. for $C_6H_{12}O_5$: OMe, 18·9%).

Examination of (XX).—(XX) (4·2 g.) was treated with benzaldehyde as for (XIV) to give crystals (2·8 g.) shown to be β-methyl-*l*-xyloside [identical with (XV)] and a syrup shown by the same method as before to be 3 : 4-benzylidene β-methylarabinoside (1·7 g.).

Thus (XX) consists of approximately 65% β-methyl-*l*-xyloside and 35% β-methyl-*l*-arabinoside.

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UNITED COLLEGE, THE UNIVERSITY, ST. ANDREWS.
UNIVERSITY OF LONDON, KING'S COLLEGE.

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213. *Electrometric Titrations of Weak Acids and Bases in Aqueous Solution.*

By D. O. Jordan and H. F. W. Taylor.

A method is described for the determination of the amount of alkali bound by water during the electrometric titration of a weak acid with alkali. The method is demonstrated by the determination of the pK_a' values of *p*-aminobenzenesulphonamide and of benziminazole and is equally applicable to the titration of weak bases with acid.

The determination of non-thermodynamic dissociation constants in aqueous solution by electrometric titration presents few difficulties provided that the region in which the titration is carried out falls within the limits pH 4·0—10·0. Outside this range complications arise and corrections must be applied to the pH titration curves for the volumes of acid or alkali which fail to react.

The necessity for such a correction was recognised by Cohn, Gross, and Johnson (*J. Gen. Physiol.*, 1919—1920, **2**, 145) and more clearly by Tague (*J. Amer. Chem. Soc.*, 1920, **42**, 173); they determined the volume of alkali required to bring a solution of a weak acid to a given pH and deducted therefrom the volume of alkali needed to bring an equal quantity of water to the same pH, as determined experimentally by a blank titration. This method has been used extensively (see, *e.g.*, Kirk and Schmidt, *J. Biol. Chem.*, 1929, **81**, 237; Albert and Goldacre, *Nature*, 1942, **149**, 245; Fletcher, Gulland, and Jordan, *J.*, 1944, 33) but, as pointed out by Cohn and Berggren (*J. Gen. Physiol.*, 1924—1925, **7**, 45), the correction so obtained is too small, since at any given pH the ionic strength is greater in the titration of the weak acid than in the blank, by virtue of the alkali bound by the weak acid.

Other workers have used conductance ratios (Harris, *J.*, 1923, **123**, 3294; *Proc. Roy. Soc.*, 1923—1924, *B*, **95**, 440; *Nature*, 1925, **115**, 119) or activity coefficients (see, *e.g.*, Greenstein, *J. Biol. Chem.*, 1931, **93**, 479; Cohn, Green, and Blanchard, *J. Amer. Chem. Soc.*, 1937, **59**, 509) to calculate, from the pH of the solution being titrated, the volume of alkali to be deducted. This procedure introduces a further error unless the cell employed involves no liquid junction. The liquid-junction potential existing between the dilute solution being titrated and a saturated potassium chloride bridge is greater at the extremes of pH than in neutral solution (Burton, Hamer, and Acree, *J. Res. Nat. Bur. Stand.*, 1936, **16**, 575; Hamer and Acree, *ibid.*, 1936, **17**, 605; and confirmed in this paper). The ensuing variation in the titration curve is not allowed for in the calculation, and gives rise to considerable errors when applying the correction.

It was concluded by Schmidt (" The Chemistry of the Amino-acids and Proteins," Baillière, Tindall and Cox, 1938, p. 605) and by Cannan (*Chem. Revs.*, 1942, **30**, 395) that an experimental determination of the correction is to be preferred and that it should be carried out under as nearly as possible the same experimental conditions, as regards ionic strength, as in the actual titration. This procedure is tedious since it involves the performance of a large number of blank experiments, and the following method was therefore evolved in which corrections for a series of titrations can be obtained from a single experimentally determined blank titration curve.

The Correction for the Titration of Weak Acids.—(For brevity, this discussion is restricted to the titration of weak acids; it applies equally to that of weak bases.) A solution of the weak acid, of volume V_a, is titrated with standard alkali. The titration is repeated, the same quantity of pure water being used, and the volume of alkali plotted against pH. At any given pH above 10·0, let the volumes of alkali in the two titrations be V and V_b (the latter being obtained from the curve), and the ionic strengths I and I_b respectively. Owing to the different volumes $(V_a + V)$ and $(V_a + V_b)$ respectively, and the different ionic strengths of the two solutions, a volume and an activity correction must be made to V_b before it is deducted from V to give the quantity of alkali, v, used to neutralise the acid. Hence

$$V'_b = \frac{V_b(V_a + V)f_b}{(V_a + V_b)f} \text{ and } v = V - V_b'$$

where f and f_b are the activity coefficients of the hydroxyl ion in the solution of the weak acid and the blank, respectively, and V_b' is the desired corrected value of V_b. By introducing the Debye–Hückel equation $(-\log f_{OH} = 0{\cdot}5\sqrt{I})$ we obtain $\log f_b - \log f = 0{\cdot}5\,(\sqrt{I} - \sqrt{I_b})$ or

$$\frac{f_b}{f} = \text{antilog}\,[0{\cdot}5(\sqrt{I} - \sqrt{I_b})]$$

and hence

$$V'_b = V_b \frac{V_a + V}{V_a + V_b} \text{antilog}\,[0{\cdot}5(\sqrt{I} - \sqrt{I_b})] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1$$

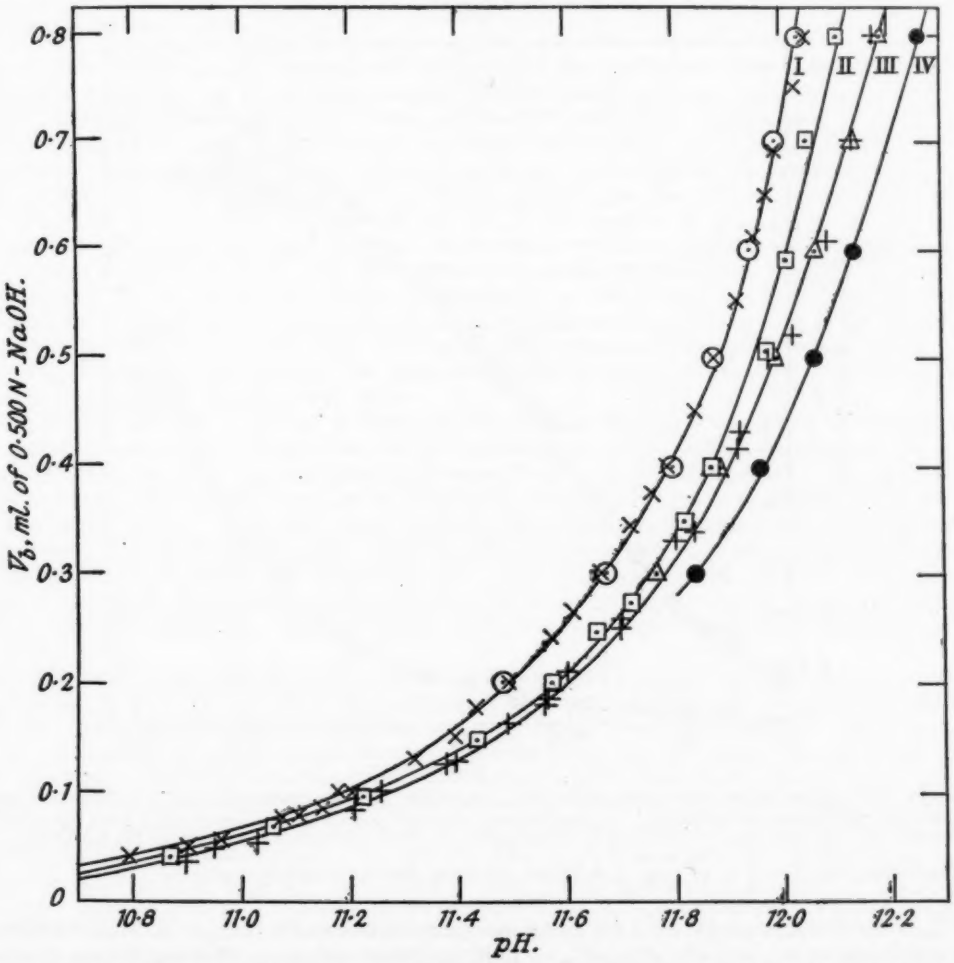
Discussion.—Experimental justification for the introduction of the Debye–Hückel equation has been obtained by using the cell $H_2Pt|NaOH, H_2O||KCl$ (satd.) in agar$||KCl$(M), Hg_2Cl_2(satd.)$|Hg$ (I) at 25°, by titrating pure water (20·0 ml.) and a solution of sodium chloride (0·0293 g. in 22·0 ml.) with 0·5M-sodium hydroxide. The results are shown in Fig. 1, curves II and I, respectively. The latter curve has also been calculated from the former by using the equation

$$-\Delta\,\text{pH} = \log \frac{(22 + V_b)}{(20 + V_b)} + 0{\cdot}5(\sqrt{I_{\text{I}}} - \sqrt{I_{\text{II}}}) \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

which has been derived on the same basis as equation (1). I_I and I_{II} are the ionic strengths in the solution with and without sodium chloride respectively. It will be seen that the experimental and the calculated curve are in excellent agreement. The use of extended forms of the Debye–Hückel limiting equation makes no significant difference in the calculated values.

The value of 282 mv. for the potential of the normal calomel electrode was obtained at 25° by using 0·05M-potassium hydrogen phthalate (pH 3·97; Clark, " The Determination of Hydrogen Ions," The Williams and Wilkins Co., Baltimore, 1928, p. 485). This potential includes the two liquid-junction potentials existing in cell I, of which that between the saturated potassium chloride bridge and the solution being titrated will vary with the pH. In alkaline solution this liquid-junction potential opposes that of the cell, thus reducing the

FIG. 1.



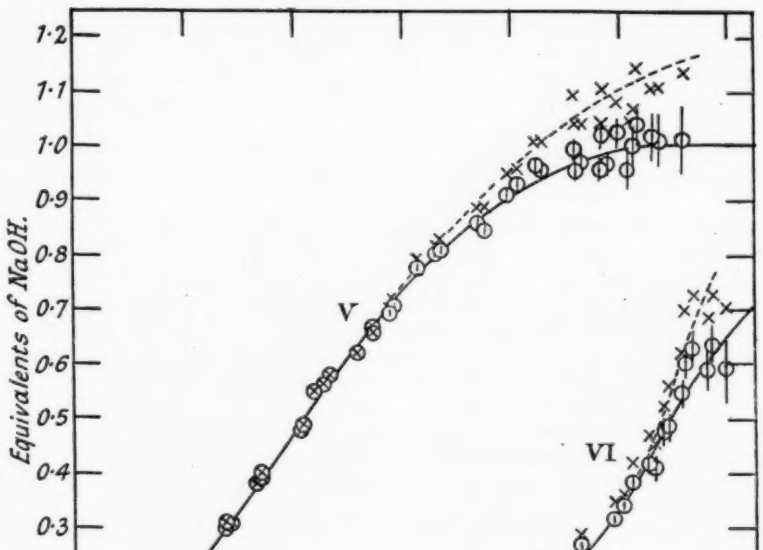
Titration curves for : I, 22·0 *ml. of water containing* 0·0293 *g. of* NaCl *using agar–calomel half-cell, experimental values* ×, *values calculated by equation* (2) *from curve* II ⊙ ; II, 20·0 *ml. of water, using agar–calomel half-cell, experimental values* ⊡ ; III, 22·0 *ml. of water containing* 0·0293 *g. of* NaCl, *using* Ag|AgCl *half-cell, experimental values* + ; *values calculated by equation* (2) *from curve* IV △ ; IV, 20·0 *ml. of water, calculated values* ●.

apparent pH, whereas in acid solution it augments the cell potential and the apparent pH is increased. The extent of the variation in alkaline solutions is seen by comparing curves II and IV (Fig. 1), the latter having been calculated from the equation $pH = pK_w + \log M_{NaOH} f_{OH'}$, on the assumption that $pH = -\log a_{H_3O^+}$ and that $f_{OH'} = f_{NaOH}$. In order to show that the discrepancy between curves II and IV could not be due either wholly or in part to a peculiarity of the agar bridge, the titration of water by use of cell I has been repeated, an aqueous saturated potassium chloride bridge being used with two reproducible liquid junctions. The results of this titration were identical with those given in curve II. This variation has also been confirmed by repeating the titration of water (22·0 ml.) in the presence of sodium chloride (0·0293 g.) with 0·5M-sodium hydroxide and using the cell H_2Pt|NaOH, NaCl,H_2O,AgCl (satd.)|Ag (II) at 25°, which contains no liquid junction. The results are given in curve III, Fig. 1 [also calculated from curve IV by using equation (2)], and the discrepancy between this curve and curve I, as between curves IV and II, is attributed to variations

in the liquid-junction potential and to the different assumptions on which the pH scales of curves I and II, III, and IV have been based.

The Use of the Correction Method.—To demonstrate the method of correction, two weak acids, *p*-aminobenzenesulphonamide and benziminazole, have been titrated with alkali. The results of these experiments are shown in Fig. 2. It will be seen that the relation between v and pH is in good agreement with Henderson's equation, and that the use of $V_b(V_s + V)/V_s + V_b)$ in place of V'_b above pH 11·0 leads to appreciable errors. The result for *p*-aminobenzenesulphonamide (curve V) shows that the inadequately corrected curve does not tend to a limit at 1·0 equivalent, a fact of considerable importance in the interpretation of the dissociation curve of a complex substance showing an unknown number of overlapping dissociations. The result for benziminazole (curve VI) shows that an error in pK'_a may also result.

FIG. 2.



Titration curves of: V, p-*aminobenzenesulphonamide* ($pK'_{a_2} = 10{\cdot}58$); VI, *benziminazole* ($pK'_{a_2} = 12{\cdot}30$). *Smooth curves calculated from the Henderson equation;* ⊙, *equivalents calculated from* $V - V_b'$ [*the vertical lines through these points represent the error (in equivalents) produced by a variation of* ±0·01 *pH unit when applying the correction*]; ×, *equivalents calculated from* $V - \left[V_b \frac{V_s + V}{V_s + V_b}\right]$, *a broken line being drawn through these points.*

The pK'_a values obtained at 25° are: for *p*-aminobenzenesulphonamide $pK'_{a_2} = 10{\cdot}58$ (in 0·0227M-solution) [cf. Albert and Goldacre (*loc. cit.*) who give $pK'_{a_2} = 10{\cdot}20$ (in 0·025M-solution); Bell and Roblin (*J. Amer. Chem. Soc.*, 1942, **64**, 2905), 10·43; Fox and Rose (*Proc. Soc. Exp. Biol. Med.*, 1942, **50**, 142), 10·5; Cook, Heilbron, Reed, and Strachan (*J.*, 1945, 861), 10·65], and for benziminazole $pK'_{a_2} = 12{\cdot}3$ (in 0·0385M-solution).

EXPERIMENTAL.

The experimental procedure was similar to that described by Fletcher, Gulland, and Jordan (*loc. cit.*). The saturated potassium chloride in agar bridges were prepared in narrow glass tubing, a 3% agar solution being used. The aqueous potassium chloride bridge contained two liquid junctions of the type described by Coates (*J.*, 1945, 489).

The silver–silver chloride electrodes were prepared according to Brown (*J. Amer. Chem. Soc.*, 1934, **56**, 646), with the additional precaution of plating the platinum wires with gold before the silver was deposited in order to avoid the possibility of error due to the adsorption of hydrogen gas or ions. The standard potential was taken as 223 mv., a value confirmed by measuring the e.m.f. of the cell, $H_2Pt|HCl$ (0·5M), AgCl (satd.)||Ag at 25°. The activity coefficient of 0·5M-hydrochloric acid was taken as 0·77 (MacInnes, "The Principles of Electrochemistry," Reinhold Publishing Corporation, New York, 1939, p. 185). Two electrodes were used in all titrations.

For the calculation of curve IV (Fig. 1) the following data were used: $pK_w = 14{\cdot}01$ at 25° (Harned and Hamer, *J. Amer. Chem. Soc.*, 1933, **55**, 2194), f_{NaOH} at 25° = 0·899 at 0·00997M, 0·858 at 0·0201M, 0·803 at 0·0525M (MacInnes, *op. cit.*, p. 155).

The water used was laboratory distilled water, redistilled in an all-"Pyrex" apparatus from dilute phosphoric acid, and

condensed in a counter stream of carbon dioxide-free air. The *p*-aminobenzenesulphonamide was obtained from British Drug Houses Limited, and was twice recrystallised from aqueous alcohol; m. p. 165—166°. The benziminazole was prepared as described in *Organic Syntheses* (1939, **19**, 12) and was twice recrystallised from water; m. p. 171—172°.

It is a pleasure to record our thanks to Professor J. M. Gulland, F.R.S., for his interest and encouragement, and to Imperial Chemical Industries Limited for the loan of apparatus.

UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, August 28th*, 1945.]

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214. *Schmidt's so-called "1 : 4-Dihydrocarbazole."*

By (MISS) B. M. BARCLAY, NEIL CAMPBELL, and ROBERT S. GOW.

The substance given in the literature as 1 : 4-dihydrocarbazole is shown to be a mixture containing more than 50% of carbazole.

By the reduction of carbazole with sodium and boiling amyl alcohol Zanetti (*Ber.*, 1893, **26**, 2006) obtained mainly tetrahydrocarbazole, but by the same method Schmidt and Schall (*Ber.*, 1907, **40**, 3226) isolated besides carbazole and tetrahydrocarbazole a substance, m. p. 228—229°, which they regarded as 1 : 4-dihydrocarbazole. It resembled carbazole in many of its physical properties, but Schmidt and Schall concluded that it was a distinct chemical entity because of the *N*-nitroso-compound, which melted with decomposition at 72—73° (*N*-nitrosocarbazole, m. p. 82° without decomposition), and the picrate, which separated in russet-brown elongated prisms, m. p. 179—180° (carbazole picrate, bright red needles, m. p. 186—187°). It seemed to us that this evidence was inconclusive and that the above results were best explained by the presence of a considerable quantity of carbazole in the so-called dihydrocarbazole, especially since acetylation was stated to give carbazole, and the percentage of hydrogen was found to be 5·96 instead of 6·51 required for dihydrocarbazole. Indeed, Schmidt and Schall admitted that traces of carbazole were present even in the purest samples of "dihydrocarbazole," but they followed this with the puzzling statement that their analyses agree best with a compound of equimolecular quantities of carbazole and dihydrocarbazole in the form of mixed crystals. We have therefore repeated and amplified their work.

The first product obtained by pouring the amyl alcohol solution into water was stated by Schmidt and Schall to consist mainly of carbazole, but we were unable to distinguish its properties and those of its picrate from those given for "dihydrocarbazole" and its picrate respectively. A second product was obtained by distilling off most of the amyl alcohol; by repeated crystallisation of this from toluene, glacial acetic acid, or ethyl alcohol, "dihydrocarbazole," m. p. 229°, was obtained with great loss in yield. Further crystallisation and chromatographic purification did not raise the m. p., and analyses of several samples gave substantially the same results as those of Schmidt and Schall (*loc. cit.*). All samples gave with sulphuric and nitric acids the blue colour characteristic of carbazole, and crystallised from alcohol in rhombic or hexagonal plates with the same profile angles as carbazole. The substance, therefore, seems to contain a considerable proportion of carbazole.

The *N*-nitroso-derivative melted over a much wider range than stated by Schmidt and Schall, and the attendant decomposition may well be due to the presence of a compound such as *N*-nitrosotetrahydrocarbazole [m. p. 33—35° (decomp.)], the main component probably being *N*-nitrosocarbazole. The picrate, although homogeneous in appearance under the microscope, also melted over a wider range than found by Schmidt and Schall and is clearly a mixture, since the picrates of carbazole derivatives melt sharply. An examination of the picrates, styphnates, and *s*-trinitrobenzene derivatives of carbazole, tetrahydrocarbazole, and "dihydrocarbazole" showed that the m. ps. and colours of the "dihydrocarbazole" derivatives were intermediate between those of carbazole and tetrahydrocarbazole. Moreover, mixtures of carbazole (2 parts) and tetrahydrocarbazole (1 part) gave molecular compounds similar in colour and m. p. to those of the corresponding derivatives of "dihydrocarbazole." These facts suggested that "dihydrocarbazole" is a mixture of carbazole and tetrahydrocarbazole, but this was excluded by the low m. p. of such a mixture and by its quick separation into pure components merely by crystallisation from alcohol.

The presence of carbazole in "dihydrocarbazole" was proved by the absorption of approximately 1 mol. of hydrogen on hydrogenation with Adams's catalyst. In all such experiments carbazole was isolated in over 50% yield in addition to an unidentified oily product, and in two a considerable quantity of tetrahydrocarbazole was obtained. It would seem therefore as if reduction gave products which were easily separated from carbazole, but it was possible that carbazole formation was due to disproportionation of dihydrocarbazole, just as the methyl ester of Δ^1-tetrahydroterephthalic acid with hydrogen in the presence of palladium (but not platinum) yields a mixture of the esters of terephthalic and hexahydroterephthalic acids (Zelinski, *Ber.*, 1911, **44**, 2305). We found, however, that with the Adams's catalyst no disproportionation occurred, only a mixture of the esters of the hexahydroterephthalic acids being obtained, and conclude that the carbazole isolated from "dihydrocarbazole" is not due to dehydrogenation.

Acetylation of "dihydrocarbazole" gave conflicting results. In one experiment *N*-acetylcarbazole was isolated in poor yield, in others only unchanged material, while Schmidt and Schall obtained carbazole. It is a little difficult to understand the inability of "dihydrocarbazole" to give *N*-acetylcarbazole under conditions in which carbazole is readily acetylated, but Schmidt and Schall's explanation of their result as due to the ease of oxidation of dihydrocarbazole is improbable.

From the above experiments we feel justified in concluding that the "dihydrocarbazole" of Schmidt and Schall is a mixture containing over 50% of carbazole. We have not been successful in identifying the other component (or components). A mixture or molecular compound of carbazole and a dihydrocarbazole would agree with the analytical and hydrogenation results, but would not contain sufficient hydrogen to account for the observed fact that one molecule of chloranil is completely reduced to the quinol by one molecule of "dihydrocarbazole."

Experimental.

Unless otherwise stated, the preparation, purification, and properties are those given in the literature. The purity of compounds was checked by the sharpness of their m. ps. on a Fuchs micro-m. p. apparatus (*Mikrochim. Acta*, 1937, **2**, 317); sublimation was also detected on this apparatus. Analyses were done by Drs. Weiler and Strauss, Oxford.

In all the chromatographic adsorption experiments, aluminium oxide (Brockmann) was used as absorbent, benzene as solvent, and benzene (3 parts)–light petroleum (b. p. 100—120°, 1 part) as developer.

Profile angles of crystals [A. C. Shead, *Ind. Eng. Chem.* (*Anal.*), 1937, **9**, 496] were measured by means of a microscope provided with an ocular with cross-wires and a graduated rotating stage. A suspension of the crystals to be measured was placed on a microscope slide, the crystals were allowed to settle, and the mother liquor was drained off. Several crystals from each sample were measured. The measurements are correct to one degree.

Preparation of "Dihydrocarbazole."—Carbazole was reduced with sodium and amyl alcohol (b. p. 128—132°) by the method of Schmidt and Schall (*loc. cit.*). The product obtained when the mixture was poured into water was crystallised thrice from alcohol. It formed rhombic plates with profile angles 107° and 73° (see below) and m. p. 226—228°. The picrate formed russet-brown elongated prisms, m. p. 175—180° (softening at 150°). The product therefore has the properties of "dihydrocarbazole" given below.

Crude "dihydrocarbazole" obtained by evaporating the amyl alcohol to 200 c.c. was washed with water until all traces of alkali had been removed, and was then crystallised to constant m. p. One sample crystallised thrice from benzene and then four times from toluene had m. p. 229°, while another after chromatographic purification had the same m. p. which was not raised by crystallisation from glacial acetic acid. A third sample, prepared from the picrate which had been crystallised three times from benzene saturated with picric acid, had m. p. 226—227° after crystallisation from benzene. The three samples gave the following analyses. (1) C, 85·2; H, 5·86. (2) C, 85·1; H, 5·57. (3) C, 85·5; H, 5·89. Other purified specimens gave the following figures: C, 84·9, 85·2; H, 5·78, 5·92. These results show decisively that the substance is not dihydrocarbazole (Calc. for $C_{12}H_{11}N$: C, 85·16; H, 6·56%), and probably not an equimolecular mixture of carbazole and dihydrocarbazole (Calc. for $C_{24}H_{20}N_2$: C, 85·66; H, 6·01%).

"Dihydrocarbazole" crystallised from alcohol in transparent rhombic plates (profile angles, 107° and 73°) and to a smaller extent in hexagonal plates (profile angles, two of 107° and four of 127°). The same results were obtained with pure carbazole except that the crystals were better defined.

The substance gave many of the colour reactions of carbazole: blue with sulphuric and nitric acids or with isatin in sulphuric acid; carmine red with benzoquinone in glacial acetic acid with a little sulphuric acid; but red on fusion with oxalic acid (carbazole, blue).

Derivatives of "Dihydrocarbazole," etc.—The nitroso-derivative of "dihydrocarbazole" melted over a range, 60—73° (decomp.), whereas *N*-nitrosocarbazole melted sharply at 82° (no decomp.). *N-Nitrosotetrahydrocarbazole* was prepared by dissolving tetrahydrocarbazole (1·5 g.) in ether (30 c.c.), glacial acetic acid (10 c.c.), and water (20 c.c.), and adding sodium nitrite (1·5 g.) with shaking. The ether layer was washed with water, sodium carbonate solution, and water, dried ($CaCl_2$), and finally evaporated under reduced pressure. The nitroso-compound separated as yellow crystals which were purified by washing with methyl alcohol; m. p. 33—35° (decomp.) (Found: N, 13·0. $C_{12}H_{12}ON_2$ requires, N, 14·0%).

Picrates. That of "dihydrocarbazole" formed russet-brown elongated prisms, m. p. 165—185° (Schmidt and Schall give 179—180°); of carbazole, bright red needles, m. p. 186°; of tetrahydrocarbazole, chocolate brown elongated prisms, m. p. 144°.

s-*Trinitrobenzene derivatives.* That of "dihydrocarbazole" formed reddish-brown elongated prisms, m. p. 175—188°; of carbazole, bright orange needles, m. p. 199°. The trinitrobenzene *derivative* of tetrahydrocarbazole formed red needles, m. p. 159° (Found: N, 14·7. $C_{18}H_{14}O_6N_4$ requires N, 14·6%).

Styphnates. That of "dihydrocarbazole" formed orange elongated prisms which sublimed in yellow needles, m. p. 165—175°; of carbazole, orange-red prisms, subliming in yellow needles, m. p. 179°. The *styphnate* of tetrahydrocarbazole formed reddish-brown elongated prisms (benzene), m. p. 152—154° (Found: N, 13·4. $C_{18}H_{16}O_8N_4$ requires N, 13·5%). All these substances appeared to be homogeneous under the microscope.

Catalytic Hydrogenation of "Dihydrocarbazole," etc.—The apparatus was calibrated by noting the fall in pressure from 60 lb./sq. in. when 1/100 mol. of benzoin was reduced to hydrobenzoin with 0·1 g. of Adams's platinum catalyst in 100 c.c. of glacial acetic acid. A fall of 8 lb. indicated absorption of 1/100 mol. of hydrogen. All reductions were carried out with the above quantities. "Dihydrocarbazole" (1·7 g.) absorbed 1/100 mol. of hydrogen rapidly. From the solution were isolated 0·6 g. of carbazole, m. p. 232—237°, and 0·9 g. of a brown oil, which gave a bright red colour with concentrated sulphuric acid but no blue colour on the further addition of nitric acid. Efforts to purify the oil by crystallisation and chromatographic adsorption failed. In two other experiments more than 50% of carbazole was obtained, with 0·4 g. of tetrahydrocarbazole, identified by m. p., mixed m. p., and picrate.

Under the same conditions carbazole was not reduced, but tetrahydrocarbazole absorbed 1/100 mol. of hydrogen to give an oily product.

Δ^1-Tetrahydroterephthalic acid [p-*nitrobenzyl* ester, prisms (glacial acetic acid), m. p. 185—187° (Found: N, 6·33. $C_{22}H_{20}O_8N_4$ requires N, 6·4%)] was converted into the dimethyl ester and hydrogenated as above. The solution was evaporated to small bulk after 1/100 mol. of hydrogen had been absorbed, and water added. An oil separated which was washed several times with water and then hydrolysed with a mixture of methyl alcohol and sodium hydroxide. Acidification, followed by partial evaporation of the solution, gave *trans*-hexahydroterephthalic acid, m. p. *ca.* 300° (Found: C, 56·1; H, 6·90. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%). From the solution a small quantity of the *cis*-acid, m. p. 167—169°, was obtained. No terephthalic acid, easily distinguished from the above *trans*-acid by its insolubility in hot water and the appearance of its sublimate, was detected.

Acetylation Experiments.—Acetylation of carbazole with acetic anhydride containing a trace of sulphuric acid gave after 1 hour's heating followed by addition of water an excellent yield of *N*-acetylcarbazole, m. p. 76° (Boeseken, *Rec. Trav. chim.*, 1912, **31**, 350). Tetrahydrocarbazole under these conditions gave a poor yield of the acetyl compound, unless very pure tetrahydrocarbazole and redistilled acetic anhydride were used. "Dihydrocarbazole" gave unsatisfactory and conflicting results. In one experiment *N*-acetylcarbazole was isolated in poor yield from the oily product, while in others only unchanged material was found.

Acetic anhydride without sulphuric acid did not attack carbazole even after refluxing for 5 hours, but gave with

tetrahydrocarbazole a 70% yield of *N*-acetyltetrahydrocarbazole, b. p. 210—230°/19 mm., m. p. 73—74° (Perkin and Plant, *J.*, 1921, **119**, 1832). The only product obtained by similar treatment of " dihydrocarbazole " was unchanged material.

Chloranil Dehydrogenation.—" Dihydrocarbazole " (0·505 g.; 0·003 g.-mol.) was refluxed with chloranil (0·733 g.; 0·003 g.-mol.) for 27 hours in 15 c.c. of sulphur-free xylene. At least 24 hours were necessary for complete dehydrogenation. Carbazole, identified by its m. p., mixed m. p., and picrate, was obtained in 83% yield. A second experiment gave a 90% yield of crude and 80% of pure carbazole. In both experiments the chloranil was completely used up. 1 : 4-Dihydronaphthalene under the same conditions was dehydrogenated to naphthalene (70% yield) in 5 hours.

THE UNIVERSITY, EDINBURGH. [*Received, February 12th*, 1946.]

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215. *Some Derivatives of Catechol and Pyrogallol. Part I.*

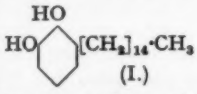
By ROBERT D. HAWORTH and DAVID WOODCOCK.

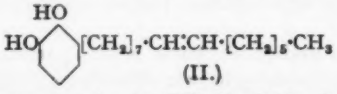
In view of the vesicancy attributed to catechol derivatives occurring in natural lacquers, a number of 3- and 4-acyl- and -alkyl-catechols containing from C_4 to C_{18} side chains have been synthesised. A similar range of 4-acyl- and -alkyl-pyrogallols have been prepared.

None of the compounds exhibit marked vesicancy.

CERTAIN species of the *Rhus*, *Melanhorrhœa*, and *Semecarpus* families are the common sources of lacquers. Contact with these plants produces a typical dermatitis, and some fatal cases of poisoning have been reported. The chemistry of the lacquers has been investigated by several workers, and in particular by Majima (*Ber.*, 1907, **40**, 4392; 1909, **42**, 1419, 3664; 1912, **45**, 2727; 1913, **46**, 4080, 4089; 1915, **48**, 1593, 1597, 1603, 1606; 1920, **53**, 1907; 1922, **55**, 172, 191) who claimed that the skin irritant properties resided in an oily fraction which was purified by distillation in a high vacuum. The active principles, which vary in constitution with the origin of the lacquer, are catechol derivatives with lengthy and unsaturated side chains, but it is probable that the purified distillates contain a number of closely related compounds differing in the degree of unsaturation of the side chain.

Urushiol, which occurs in Chinese and Japanese lacquers (*Rhus vernicefera*), in Indian marking nut (*Semecarpus anacardium*) (Pillay and Siddiqui, *J. Ind. Chem. Soc.*, 1931, **8**, 517), and in the leaves and branches of poison ivy (*Rhus toxicodendron*) (Hill, Mattacocci, and Graham, *J. Amer. Chem. Soc.*, 1934, **56**, 2736) is probably a mixture of (I), (II), and (III) and possibly more highly unsaturated compounds of the same carbon skeleton.


(I.)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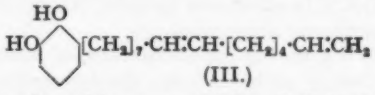
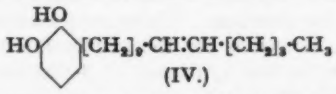

(III.)

As the composition of the oil approximates to (III) the latter is usually referred to as urushiol and (I) and (II) are regarded as tetra- and dihydro-urushiol respectively. These conclusions are supported by oxidation and bromination experiments, by the observation that catalytic reduction of crude urushiol gives high yields of the crystalline tetrahydro-derivative (I), and by the synthesis of the dimethyl ether of (I).

Recently Backer and Haack (*Rec. Trav. chim.*, 1938, **57**, 225) have isolated a crystalline substance named renghol from renghos fruit (*Semecarpus heterophylla*). Structure (IV), isomeric with dihydrourushiol (II), has been established by ozonisation and by an additional synthesis of the dimethyl ether of dihydrorenghol.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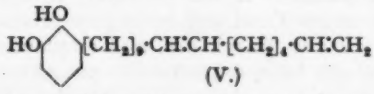
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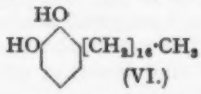
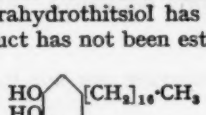

(VI.)

A complexity similar to that observed with urushiol applies to the active oil, laccol, which has been isolated from Indochinese lac from Tonkin (*Rhus succedanea*), Formosa lac (*Semecarpus vernicifera*), Tsuti-urushi lac (*Rhus ambigua* or *orientalis*) and from the fruit of *Gluta Renghos* (Bertrand, Backer, and Haack, *Bull. Soc. chim.*, 1939, **6**, 1690). The experiments of Majima suggest that laccol is composed of (V) together with di- and tetra-hydro-derivatives, and reduction of crude laccol gives high yields of tetrahydrolaccol (VI) which has been synthesised. More recently Brooks (*Actualités Scientifiques et Industrielles*, 1934, No. 94; *Bull. Soc. chim.*, 1933, **53**, 432) has described laccol as a crystalline solid, m. p. 23°.

The irritant properties of Burmese lac (*Melanorrhœa usitata*) according to Majima are due to an oil, thitsiol, containing a mixture of closely related 4-alkylated catechol derivatives differing in degree of unsaturation of the side chain, but the inferior yields of tetrahydrothitsiol obtained by catalytic reduction indicate that the oil is also contaminated with much neutral and possibly unrelated material. The structure (VII) for tetrahydrothitsiol has been confirmed synthetically, but the position of the double bonds in the natural product has not been established.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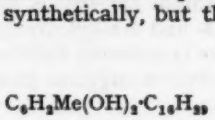
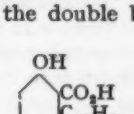
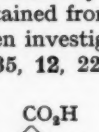

(VIII.)

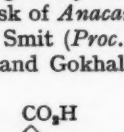

(IX.)

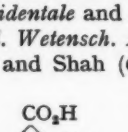
The Indochinese lac from Cambodia, unlike that from Tonkin, is derived from *Melanorrhœa laccifera*. Bertrand and Brooks (*Compt. rend.*, 1933, **197**, 661) isolated the active principle, moreakol, as a solid, m. p. 28°.

containing two double bonds, which is isomeric with thitsiol and laccol and which probably contains a nuclear substituted methyl group as in (VIII). The orientation of the nucleus, apart from the catechol grouping, and the position of the ethylenic linkages in the side chains have not been determined.

Two naturally occurring salicylic acid derivatives are known to have skin irritant action. Anacardic acid, obtained from the husk of *Anacardium occidentale* and *A. orientale* and from the shell of the cashew nut have been investigated by Smit (*Proc. K. Akad. Wetensch. Amsterdam*, 1931, **34**, 165), Pillay (*J. Ind. Chem. Soc.*, 1935, **12**, 226, 231), and Gokhale, Patel, and Shah (*Current Science*, 1940, **9**, 362). It probably has


(X.)


(XI.)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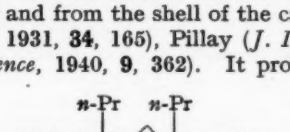
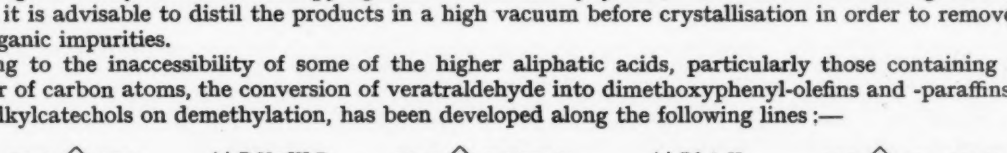

(XIII.)

structure (IX) or (X), containing two ethylenic linkages at unknown positions in the side chain. Pelandjauic acid, obtained from the wood of *Pentaspadon motleyi* Hook, and investigated by van Rombergh and van Veen (*Proc. K. Akad. Wetensch. Amsterdam*, 1929, 1204; 1930, 589, 690) is regarded as a mixture of (XI) and (XII), but neither the orientation of the substituents nor the positions of the two ethylenic linkages in the side chain has been established.

The irritant properties of a few synthetic phenols have been reported; Kawai (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1927, **6**, 53) states that 3-geranylcatechol, an oil obtained by the action of heat on *O*-geranylcatechol, produces strong itching which lasts for several weeks, and Hurd and Parrish (*J. Amer. Chem. Soc.*, 1935, **57**, 1731) mention the activity of a number of substances such as dihexenylpyrogallol (XIII).

Several 4-acylcatechols have been prepared by Miller, Hartung, Rock, and Crossley (*J. Amer. Chem. Soc.*, 1938, **60**, 7) and Majima (*Ber.*, 1915, **48**, 1599) by condensing catechol with aliphatic acids in the presence of zinc chloride (Nencki reaction), and the Fries reaction has been employed by Rosenmund and Lohfert (*Ber.*, 1928, **61**, 2605) for other compounds of the series. Some alkylpyrogallols have been prepared by the Nencki reaction by Hart and Woodruff (*J. Amer. Chem. Soc.*, 1936, **58**, 1957). In our hands the Nencki reaction was in general more convenient and gave high yields in the pyrogallol series. Clemmensen reduction of the ketones gave 4-alkyl-catechols and -pyrogallols in satisfactory yields, but in order to obtain good analytical results it is advisable to distil the products in a high vacuum before crystallisation in order to remove traces of inorganic impurities.

Owing to the inaccessibility of some of the higher aliphatic acids, particularly those containing an odd number of carbon atoms, the conversion of veratraldehyde into dimethoxyphenyl-olefins and -paraffins, which yield alkylcatechols on demethylation, has been developed along the following lines:—



The reactions proceeded smoothly as far as the demethylation stage where it became necessary to determine optimum conditions for each; hydriodic and hydrobromic acids were used under the three conditions described in the Experimental section. It was necessary to free all the products by distillation in a high vacuum from small amounts of catechol and high boiling by-products of the reaction. Using *o*-veratraldehyde instead of veratraldehyde, Backer and Haack (*loc. cit.*) employed these reactions for the synthesis of tetrahydrolaccol dimethyl ether, and we have explored the reactions widely in the synthesis of 3-alkylcatechol derivatives.

The vesicant properties of the alkyl phenols together with a few acyl derivatives were tested by Dr. K. Harrison by applying a 2 mm. diameter drop of 10 per cent. w/w solution in benzene, alcohol, or chloroform to the skin of the upper arm of two men, the spread of the drop being controlled to cover a circular area of 1·5 mm. diameter. None of the compounds produced vesication, but several caused erythema and the symbols E— and E in Table III indicate slight reddening and reddening respectively; the subscript numerals are the number of days which elapse before erythema is apparent. The following are the main points emerging from the investigation:

(1) Catechols are more irritant than the corresponding pyrogallol derivatives.

(2) In the 4-alkylcatechol series the members from butyl to octyl have approximately the same activity which decreases with increasing length of the side chain.

(3) In the 3-alkylcatechol series optimum activity is found in the 3-heptyl derivative, but there is no pronounced difference in the activity of 3- and 4-alkylcatechols.

(4) Acyl-catechols and -pyrogallols are completely inactive.

(5) The slight activity of 4-amylresorcinol suggests that the irritant properties are not limited to the catechol series.

Specimens of 4-butyl- and 4-heptyl-catechol were oxidised in ethereal solution with silver oxide according to the method of Willstätter *et al.* (*Ber.*, 1904, **37**, 4744; 1908, **41**, 2580; 1911, **44**, 2172). The corresponding *o*-quinones were obtained as red oils which could not be purified, but in contrast to the parent catechol derivatives they were entirely lacking in skin irritant properties.

Experimental.

I. *Nencki Reaction.*—Two methods were used. (*a*) The phenol (1 mol.), aliphatic acid (2·1 mols.), and anhydrous zinc chloride (1 mol.) were heated at 135—140° for 2 hours. The mixture was cooled and treated with dilute hydrochloric acid, and the product taken up in ether. The extract was washed three times with water in order to remove most of the unreacted phenol, and the residue from the dried ethereal solution was distilled at 0·5 mm. Unchanged acid was recovered, and after distillation the 4-acylphenol was crystallised.

(*b*) Equal weights of the phenol, aliphatic acid, and anhydrous zinc chloride were heated at 135—140° for 2 hours. The mixture was cooled and treated with dilute hydrochloric acid; if solid, the product was collected and washed well with water to remove unchanged phenol; if liquid, the lower aqueous layer was separated and the upper layer washed several times with water. The residue was taken up in ether, dried, the solvent removed, and the residue treated with light petroleum (b. p. 40—60°) which removed unreacted acid. The residue was then distilled at 0·5 mm.

This method (*b*) was introduced for the more complex acylphenols, and increased yields of these were obtained. It is probable that the yields of lower members could be increased by the use of (*b*) but this point has not been tested in many cases.

II. *Fries Reaction.*—Two methods were used. (*a*) The catechol diester (1 mol., prepared by heating catechol with 2 mols. of acid chloride until evolution of hydrogen chloride ceased), catechol (1 mol.), and aluminium chloride (2 mols.) in nitrobenzene (20 mols.) were heated at 80—100° for 2 hours. The product was cooled and decomposed with dilute hydrochloric acid, and the nitrobenzene removed in steam; the product, isolated with ether, was purified by distillation at 0·5 mm.

(*b*) The phenol (1 mol.) and aluminium chloride (1·5 mols.) were stirred in carbon disulphide (20 parts) during the gradual addition of acid chloride (1 mol.). After warming at 40—50° the solvent was removed and the residue heated at 150° for 4 hours. Dilute hydrochloric acid was added and the product, isolated with ether, was purified as in II (*a*). The properties of the new acylphenols are included in Table I together with those showing marked m. p. discrepancies from those reported in the literature.

Table I.

Acylphenol.	M. p. *ex* benzene.	Method of prep.	Yield (%).	Found (%). C.	Found (%). H.	Required or calc. (%). Formula.	Required or calc. (%). C.	Required or calc. (%). H.
4-Heptanoylcatechol	93—94° Lit (i) gives 79°.	II*b*	50	70·1	8·2	$C_{13}H_{18}O_3$	70·3	8·1
4-*Nonanoylcatechol*	92—93	II*a*	40	72·3	9·1	$C_{15}H_{22}O_3$	72·0	8·8
4-*Undecanoylcatechol*	105	I*b*	15	73·7	9·7	$C_{17}H_{26}O_3$	73·4	9·3
4-*Dodecanoylcatechol*	97—98	I*b*	20	73·7	10·0	$C_{18}H_{28}O_3$	74·0	9·6
4-*Tetradecanoylcatechol*	98—99	I*b*	20	74·6	10·1	$C_{20}H_{32}O_3$	75·0	10·0
4-*Hexadecanoylcatechol*	99—100	I*b*	10	75·7	10·4	$C_{22}H_{36}O_3$	75·8	10·3
4-Octadecanoylcatechol	100—101 Lit (ii) gives 70°.	I*b*	10	76·2	10·7	$C_{24}H_{40}O_3$	76·6	10·6
4-Butyroylpyrogallol	90—91 Lit (iii) gives 101°.	I*a*	60	61·0	6·2	$C_{10}H_{12}O_4$	61·2	6·1
4-Hexanoylpyrogallol	72—74 Lit (iii) gives 86°.	I*a*	50	64·1	7·3	$C_{12}H_{16}O_4$	64·3	7·1
4-*Octanoylpyrogallol*	73—74	I*a*	40	66·5	8·2	$C_{14}H_{20}O_4$	66·7	8·0
4-*Undecanoylpyrogallol*	76—77	I*a*	35	68·7	8·9	$C_{17}H_{26}O_4$	69·4	8·8
4-*Dodecanoylpyrogallol*	76—77	I*a*	30	70·2	9·3	$C_{18}H_{28}O_4$	70·1	9·1
4-*Tetradecanoylpyrogallol*	82—84	I*a*	25	70·8	9·9	$C_{20}H_{32}O_4$	71·4	9·5
4-*Hexadecanoylpyrogallol*	89—90	I*a*	30	72·2	10·0	$C_{22}H_{36}O_4$	72·5	9·9
4-*Octadecanoylpyrogallol*	91—93	I*a*	25	72·9	10·2	$C_{24}H_{40}O_4$	73·5	10·2

Lit (i) Miller, Hartung, Rock, and Crossley (*loc. cit.*).
,, (ii) Rosenmund and Lohfert (*loc. cit.*).
,, (iii) Hart and Woodruff (*loc. cit.*).

III. *Clemmensen Reduction.*—The acylphenol (1 part), amalgamated zinc (5 parts), and concentrated hydrochloric acid (5 parts) were refluxed for 24 hours. The product was extracted with ether, washed with sodium bicarbonate solution, dried, and distilled at 0·5 mm. Yields varied from 50 to 65%.

IV. *Demethylation Process.*—(*a*) *Preparation of dimethoxyphenylolefins.* The Grignard reagent, prepared from magnesium (1 mol.) and the appropriate alkyl bromide or iodide (1 mol.) in ether (10 parts), was gradually added with stirring to an ice-cold solution of veratraldehyde or *o*-veratraldehyde (6 g.) in ether. The suspension was refluxed for 2 hours and decomposed with 2N-sulphuric acid, and the ether layer was washed with sodium hydrogen sulphite solution, dried, and the solvent removed. The residual oil was heated for ½ hour with potassium hydrogen sulphate (0·7 g.) at 180°, taken up in ether, washed with dilute sodium hydroxide, the ether removed, and the product distilled at 0·5 mm.

The b. ps. gradually increase from 85°/0·5 mm. for 2 : 3-dimethoxyphenyl-Δ^1-butene to 190°/0·5 mm. for the corresponding Δ^1-pentadecene. Table II includes only the olefins and alkylveratroles which have been obtained crystalline.

Table II.

Dimethoxyphenylolefin or alkylveratrole.	M. p. *ex* alcohol.	Method of prep.	Yield (%).	Found (%). C.	Found (%). H.	Required or calc. (%). Formula.	Required or calc. (%). C.	Required or calc. (%). H.
3 : 4-*Dimethoxyphenyl-*Δ^1*-heptadecene*	40—41°	IV*a*	60	80·3	11·4	$C_{25}H_{42}O$	80·2	11·2
3 : 4-Dimethoxyphenylheptadecane (tetrahydrothitsiol dimethyl ether)	53—54	IV*b*	100	79·7	11·5	$C_{25}H_{44}O_2$	79·8	11·7
2 : 3-*Dimethoxyphenyl-*Δ^1*-pentadecene*	52	IV*a*	35	79·6	11·2	$C_{23}H_{38}O_2$	79·8	11·0
2 : 3-*Dimethoxyphenylpentadecane*	34—36	IV*b*	100	79·1	11·6	$C_{23}H_{40}O_2$	79·3	11·5

(*b*) ***Catalytic reduction.*** The dimethoxyphenylolefin (5 g.) in alcohol (10 c.c.) was shaken with 10% palladium-carbon (0·5 g.) in hydrogen until gas absorption ceased (4—12 hours depending on the activity of the catalyst). After filtration from the catalyst, the solvent was removed and the residue distilled at 0·5 mm.

(*c*) ***Demethylation.*** (i) The reduction product (5 g.) was heated in a sealed tube at 180° with hydrobromic acid (15 c.c.; *d* 1·72) and a trace of red phosphorus for 4 hours. After dilution with water the product was isolated with ether, washed with sodium bicarbonate solution, dried, and the solvent removed; the residue was fractionated at 0·5 mm. The first drops of distillate frequently contained catechol, and a high-boiling fraction was always obtained, but this has not been examined. The alkylcatechol was obtained from the intermediate fraction.

(ii) The methyl ether (5 g.) was refluxed with hydrobromic acid (40 c.c.; *d* 1·5) and glacial acetic acid (40 c.c.) for 5—6 hours. The mixture was diluted with water, and the product, isolated with ether, was washed with water and sodium bicarbonate solution, and distilled as described in (i).

TABLE III.

Alkylphenol.	M. p.	Solvent.	Method of prep.	Found (%). C.	Found (%). H.	Required or calc. (%). Formula.	Required or calc. (%). C.	Required or calc. (%). H.	Vesicancy tests.	
4-Butylcatechol	39—41° Lit (i) gives b. p. only.	Ligroin	III	72·1	8·7	$C_{10}H_{14}O_2$	72·3	8·4	E_1	E_1
4-Amylcatechol	57—59 Lit (i) gives b. p. only.	Ligroin	III or IV*c*	73·2	9·0	$C_{11}H_{16}O_2$	73·3	9·0	E_1	E
4-Hexylcatechol	Oil b. p. 145—150°/ 0·5 mm. Lit (i) gives 164°/ 5 mm.	—	III	74·1	9·3	$C_{12}H_{18}O_2$	74·2	9·3	E_1	E_1
4-Heptylcatechol	65—67 Lit (i) gives 40°.	Ligroin	III	75·0	9·7	$C_{13}H_{20}O_2$	75·0	9·6	E_1	E_1
4-Octylcatechol	57—58 Lit (i) gives 40°.	Ligroin	III	75·7	10·0	$C_{14}H_{22}O_2$	75·6	10·0	E_1	E_1
4-*Nonylcatechol*	68	Ligroin	III	75·9	10·2	$C_{15}H_{24}O_2$	76·3	10·2	E_1–	E_1–
4-*Undecylcatechol*	81—82	Ligroin	III	76·9	10·7	$C_{17}H_{28}O_2$	77·3	10·6	E_4	E_4–
4-*Dodecylcatechol*	75—76	Ligroin	III	78·0	10·5	$C_{18}H_{30}O_2$	77·7	10·8	E_1	E_4–
4-*Tetradecylcatechol*	65—67	Ligroin	III	78·1	10·9	$C_{20}H_{34}O_2$	78·4	11·1	E_4	E_4
4-*Hexadecylcatechol*	75—76	Ligroin	III	78·7	11·4	$C_{22}H_{38}O_2$	79·0	11·4	nil	nil
4-Heptadecylcatechol (tetrahydrothitsiol)	93—95 Lit (iv) gives 95°.	Acetic acid	IV*c*	79·1	11·6	$C_{23}H_{40}O_2$	79·3	11·5	E_1–	nil
4-*Octadecylcatechol*	78—79	Ligroin	III	79·3	11·6	$C_{24}H_{42}O_2$	79·5	11·6	nil	nil
3-*Butylcatechol*	33—36	Ligroin	IV*c* (i)	72·2	8·5	$C_{10}H_{14}O_2$	72·3	8·4	E_1	E_1–
3-*Amylcatechol*	34—35	Ligroin	IV*c* (ii)	73·1	9·1	$C_{11}H_{16}O_2$	73·3	9·0	nil	nil
3-*Hexylcatechol*	30—31	Ligroin	IV*c* (ii)	74·2	9·2	$C_{12}H_{18}O_2$	74·2	9·3	E_1	E_1–
3-*Heptylcatechol*	Solid at 5°	—	IV*c* (ii)	75·0	9·6	$C_{13}H_{20}O_2$	75·0	9·6	E_1	E_4
3-*Octylcatechol*	Oil b. p. 135—140°/ 0·4 mm.	—	IV*c* (ii)	75·5	9·9	$C_{14}H_{22}O_2$	75·6	10·0	E_1–	E_1–
3-Pentadecylcatechol (tetrahydrourushiol)	57—59 Lit (iv) gives 59°.	Ligroin	IV*c* (iii)	78·6	11·4	$C_{21}H_{36}O_2$	78·7	11·2	E_1	E_1–
3-Heptadecylcatechol (tetrahydrolaccol)	59 Lit (iv) gives 63°.	Ligroin	From laccol.	79·0	11·5	$C_{23}H_{40}O_2$	79·3	11·5	E_4	nil
4-Butylpyrogallol	82—83 Lit (iii) gives 88°.	Benzene	III	65·8	7·9	$C_{10}H_{14}O_3$	65·9	7·7	nil	nil
4-Hexylpyrogallol	98—99 Lit (iii) gives 104°.	Benzene	III	68·3	8·7	$C_{12}H_{18}O_3$	68·6	8·6	E_4	nil
4-Heptylpyrogallol	109—111 Lit (iii) gives 116°.	Benzene	III	69·5	9·1	$C_{13}H_{20}O_3$	69·6	8·9	E_1–	E_1
4-*Octylpyrogallol*	106—107	Benzene	III	70·6	9·5	$C_{14}H_{22}O_3$	70·6	9·2	E_1	E_1–
4-*Nonylpyrogallol*	109—110	Benzene	III	71·3	9·5	$C_{15}H_{24}O_3$	71·4	9·5	E_4	nil
4-*Undecylpyrogallol*	110—111	Benzene	III	73·0	10·3	$C_{17}H_{28}O_3$	72·8	10·0	E_1–	E_1–
4-*Dodecylpyrogallol*	109—110	Benzene	III	73·2	10·3	$C_{18}H_{30}O_3$	73·5	10·2	nil	nil
4-*Tetradecylpyrogallol* ...	112—113	Benzene	III	74·3	10·4	$C_{20}H_{34}O_3$	74·5	10·6	nil	nil
4-*Hexadecylpyrogallol* ...	116	Benzene	III	75·2	10·8	$C_{22}H_{38}O_3$	75·4	10·9	nil	nil
4-*Octadecylpyrogallol*	114—115	Benzene	III	75·9	10·9	$C_{24}H_{42}O_3$	76·2	11·1	nil	nil
4-Amylresorcinol	71—72 Lit (i) gives 71°.	Ligroin	III	73·0	9·0	$C_{11}H_{16}O_2$	73·3	8·9	E_1–	nil

Lit (i), (ii), and (iii)—as for Table I. Lit (iv), Majima (*loc. cit.*).

(iii) The ether (5 g.) was refluxed with hydriodic acid (25 c.c.; *d* 1·88) and a trace of red phosphorus for 5 hours. Water was added and the product, isolated with ether, was purified as described in (i) and (ii). The most suitable method gave yields of about 60%. Table III includes the properties of the alkylphenols.

Our thanks are due to the Experimental Station, Porton, for the physiological examination of the compounds, and to the Chief Scientific Officer, Ministry of Supply, for permission to publish the work.

THE UNIVERSITY, SHEFFIELD. [*Received, March 30th*, 1946.]

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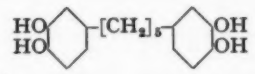
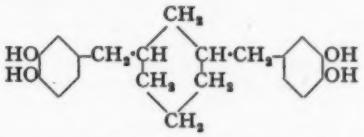
216. *Some Derivatives of Catechol and Pyrogallol. Part II.*

By ROBERT D. HAWORTH and ALEX. H. LAMBERTON.

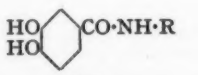
A miscellaneous selection of 4-substituted catechol derivatives containing saturated or unsaturated side chains have been prepared, and a new method has been employed for the preparation of 3-alkoxycatechols, based upon the alkylation and subsequent hydrolysis of 2 : 3-(3′-hydroxy-*o*-phenylene)dioxydioxan (VI; R = H). The compounds lack marked vesicant properties.

IN order to examine the influence of two catechol groupings on vesicancy 1 : 5-*di*-(3′ : 4′-*dihydroxyphenyl*)*pentane* (I) and 1 : 3-*di*-(3′ : 4′-*dihydroxyphenyl*)cyclo*hexane* (II) have been prepared from di-(3′ : 4′-dimethoxybenzylidene)acetone and 2 : 6-*di*-(3′ : 4′-*dimethoxybenzylidene*)cyclo*hexanone* respectively by two stage reduction and subsequent demethylation. Both substances were non-irritant to the skin.

(I.) 

 (II.)

Numerous unsuccessful attempts have been made to prepare catechol derivatives with ethylenic side chains, but amides of types (III) and (IV) have been prepared in which R represents an unsaturated radical.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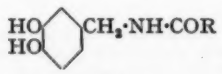
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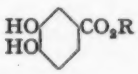
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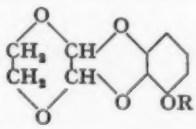 (VI.)

3 : 4-Carbonyldioxybenzoyl chloride (Barger, *J.*, 1908, **567**) reacts with allylamine and undec-10-enylamine (Krafft and Tritschler, *Ber.*, 1900, **33**, 3583) to yield N-*allyl*- (III; R = $CH_2{\cdot}CH{:}CH_2$) and N-*undec*-10-*enyl*- (III; R = $[CH_2]_9{\cdot}CH{:}CH_2$) *protocatechuic amides* respectively.

N-(3 : 4-*Dihydroxybenzyl*)*sorbic amide* (IV; R = $CH{:}CH{\cdot}CH{:}CH{\cdot}CH_3$) and *N*-(3 : 4-dihydroxybenzyl)-undec-10-enoic amide (IV; R = $[CH_2]_8{\cdot}CH{:}CH_2$) have been prepared by Einhorn's method (*Annalen*, 1905, **343**, 207) from catechol and N-*methylolsorbic amide* or *N*-methylolundec-10-enoic amide (Jones and Pyman, *J.*, 1925, 2588) respectively. These four unsaturated amides were non-irritant; *allyl protocatechuate* (V; R = $CH_2{\cdot}CH{:}CH_2$) and *undec*-10-*enyl protocatechuate* (V; R = $[CH_2]_9{\cdot}CH{:}CH_2$), prepared from 3 : 4-carbonyldioxybenzoyl chloride and allyl or undec-10-enyl alcohol (Grun and Wirth, *Ber.*, 1922, **55**, 2208) respectively, were also inactive.

Attempts to prepare 3-alkoxycatechols by the direct alkylation of pyrogallol led to a mixture of mono-, di-, and tri-alkyl derivatives, but pyrogallol carbonate has been converted into 3-methoxycatechol by the action of diazomethane and subsequent hydrolysis (Hillemann, *Ber.*, 1938, **71**, 41).

As considerable hydrolysis of the carbonate group occurred when the methylation was effected with methyl iodide and potassium carbonate in acetone solution, this method of protection was abandoned. We have found that 2 : 3-dichlorodioxan reacts with pyrogallol in warm benzene solution to give 2 : 3-(3′-*hydroxy*-*o*-*phenylene*)*dioxydioxan* (VI; R = H) in 33% yield. No difficulty was experienced in alkylation of the phenolic group, and *ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl, hexadecyl*, and *allyl* derivatives have been prepared. Hydrolysis of the dioxan group presented difficulties; the compounds were stable towards alkalis, and brown amorphous products were obtained by boiling with mineral acids. The formation of these undesirable products is probably due to the action of the liberated glyoxal on the catechol derivative and they could be avoided to a large extent by hydrolysis with hydrochloric acid in the presence of urea. In this way 3-ethoxy- and 3-propoxycatechol were prepared, but higher members were very resistant to hydrolysis and poor yields were obtained. The physiological tests show that some of these substances produce erythema, and maximum activity is observed with 3-propoxy- and 3-butoxy-derivatives.

EXPERIMENTAL.

Di-(3′ : 4′-*dimethoxybenzylidene*)*acetone*.—Veratraldehyde (20 g.), acetone (4 c.c.), and 8% sodium hydroxide (12 c.c.) were kept at 15° for 20 hours. The solid (16 g.), m. p. 118—120°, was collected, washed with alcohol, and crystallised from alcohol; light yellow plates, m. p. 122—123° (Found : C, 71·3; H, 6·3. Calc. for $C_{21}H_{22}O_5$: C, 71·2; H, 6·2%). Stobbe and Haertel (*Annalen*, 1909, **370**, 104), Dickenson, Heilbron, and Irvine (*J.*, 1927, 192), and Sugasawa and Yoshkawa

(*J.*, 1933, 1584) give m. p. 84°. In some experiments we obtained the low-melting form and the discrepancy is possibly due to dimorphism.

Reduction of Di-(3′ : 4′-dimethoxybenzylidene)acetone.—The unsaturated ketone (10 g.) in ethyl acetate (100 c.c.) was reduced in the presence of a 10% palladium–carbon catalyst during two hours. The mixture was filtered and evaporated, and the product taken up in ether (35 c.c.). The 1 : 5-di-(3′ : 4′-dimethoxyphenyl)pentan-3-one which gradually separated (4·2 g.) crystallised from alcohol in needles, m. p. 85° (Found : C, 70·2; H, 7·5. Calc. for $C_{21}H_{26}O_5$: C, 70·4; H, 7·3%). Sugasawa and Yoshkawa (*loc. cit.*) give m. p. 85°. The oxime melted at 138° as stated by Sugasawa and Yoshkawa. The ethereal mother liquor was evaporated and the residue crystallised from aqueous alcohol; needles (3·5 g.), m. p. 83—85°, were obtained. These were 1 : 5-*di*-(3′ : 4′-*dimethoxyphenyl*)*pentan*-3-*ol* (Found : C, 69·6; H, 7·8. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8%).

1 : 5-*Di*-(3′ : 4′-*dimethoxyphenyl*)*pentane*, obtained in 50% yield by Clemmensen reduction of the above ketone, crystallised from aqueous alcohol in needles, m. p. 56—57° (Found : C, 73·2; H, 8·5. $C_{21}H_{28}O_4$ requires C, 73·1; H, 8·1%).

1 : 5-*Di*-(3′ : 4′-*dihydroxyphenyl*)*pentane*.—1 : 5-Di-(3′ : 4′-dimethoxyphenyl)pentane (1·7 g.) was refluxed with hydriodic acid (20 c.c.) and phenol (7 g.) for 70 minutes in a stream of carbon dioxide. After removal of the phenol in steam an ethereal extract was washed with water and aqueous sodium thiosulphate, and evaporated to dryness. The residual *compound* crystallised from water (charcoal) in needles (0·58 g.), m. p. 129—130° (Found : C, 70·8; H, 7·1. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%).

Reduction of 2 : 6-*Di*-(3′ : 4′-*dimethoxybenzylidene*)cyclo*hexanone*.—The unsaturated ketone (Samdahl, *Centr.*, 1928, I, 2256) (5 g.) was reduced in acetic acid suspension as described above. The solvent was removed under reduced pressure and the residue crystallised from methyl alcohol. The first crop (2·7 g.), m. p. 93—95°, yielded 2 : 6-*di*-(3′ : 4′-*dimethoxybenzyl*)cyclo*hexanone* in felted needles, m. p. 112° (Found : C, 71·9; H, 7·2. $C_{24}H_{30}O_5$ requires C, 72·3; H, 7·5%), after a further crystallisation from methyl alcohol. The alcohol liquors were evaporated and the residue crystallised three times from benzene–ligroin; 2 : 6-*di*-(3′ : 4′-*dimethoxybenzyl*)cyclo*hexanol* was obtained in needles, m. p. 110—111° (Found : C, 71·7; H, 8·0. $C_{24}H_{32}O_5$ requires C, 72·0; H, 8·0%).

2 : 6-*Di*-(3′ : 4′-*dimethoxybenzyl*)-1-*methyl*cyclo*hexanol*, prepared by the action of methylmagnesium iodide on an ether–benzene solution of 2 : 6-di-(3′ : 4′-dimethoxybenzyl)*cyclo*hexanone, separated from benzene–ligroin in needles, m. p. 168—172° (Found : C, 72·7; H, 8·2. $C_{15}H_{24}O_5$ requires C, 72·4; H, 8·2%).

1 : 3-*Di*-(3′ : 4′-*dimethoxybenzyl*)cyclo*hexane*, obtained in 50% yield by Clemmensen reduction of 2 : 6-di-(3′ : 4′-dimethoxybenzyl)*cyclo*hexanone, crystallised from alcohol–ligroin in needles, m. p. 75—77° (Found : C, 74·8; H, 8·7. $C_{24}H_{32}O_4$ requires C, 74·9; H, 8·3%). All attempts to demethylate it yielded oils which could not be purified, and were non-irritant.

N-*Allylprotocatechuic Amide* (III; R = CH_2·CH:CH_2).—3 : 4-Carbonyldioxybenzoyl chloride (Barger, *loc. cit.*) (2 g.) in ether (20 c.c.) was gradually added with cooling and shaking to allylamine (1·15 g.) in ether (15 c.c.). After ½ hour N/3-hydrochloric acid (30 c.c.) was added; after shaking, the product was collected and refluxed with N-ammonia (20 c.c.) for 15 minutes. The solution was cooled, filtered, and acidified with concentrated hydrochloric acid (4 c.c.); the *amide* (III; R = CH_2·CH:CH_2) separated in needles (0·3 g.), m. p. 198—199°, which gave an intense green ferric test (Found : C, 62·5; H, 5·9. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7%).

N-*Undec*-10-*enylprotocatechuic Amide* (III; R = $[CH_2]_9$·CH:CH_2).—3 : 4-Carbonyldioxybenzoyl chloride (1 g.) in ether (10 c.c.) was added to an ice-cold solution of undec-10-enylamine (Krafft and Tritschler, *Ber.*, 1900, **33**, 3583) in ether (7 c.c.). The ethereal suspension was washed with dilute hydrochloric acid, and the collected product warmed with sodium hydroxide solution (12 c.c. of N/3) for 15 minutes on the water-bath. The cooled solution was made strongly alkaline with N-sodium hydroxide (6 c.c.), washed with ether, acidified, and the free *phenol* extracted with ether and crystallised from ether–ligroin; needles (0·4 g.), m. p. 110—111° (Found : C, 70·8; H, 9·2. $C_{18}H_{27}O_3N$ requires C, 70·8; H, 8·9%), giving an intense green ferric test, were obtained.

N-*Methylolsorbic Amide*.—Sorbic amide (2 g.), 40% formaldehyde (1·4 c.c.), potassium carbonate (0·1 g.), and water (10 c.c.) were heated on the water-bath for 2 hours. Next day the *product* was collected, washed with water, dried, and crystallised from acetone; slender needles (2 g.), m. p. 137° (Found : C, 59·6; H, 8·0. $C_7H_{11}O_2N$ requires C, 59·5; H, 7·8%), were obtained.

N-(3 : 4-*Dihydroxybenzyl*)*sorbic Amide* (IV; R = CH:CH·CH:CH·CH_3).—A solution of *N*-methylolsorbic amide (1·8 g.), catechol (1·4 g.), concentrated hydrochloric acid (5 c.c.), and alcohol (5 c.c.) was kept for 48 hours. The product, isolated with ether, was taken up in N-sodium hydroxide, recovered by acidification, and extracted with ether. After removal of the solvent the residue was triturated with water and the solid (1·7 g.) collected and dried in a vacuum. Crystallisation from acetone–benzene gave the *amide* as a microcrystalline powder, m. p. 134—136° (Found : C, 67·8; H, 6·5. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·5%).

N-(3 : 4-*Dihydroxybenzyl*)*undec*-10-*enoic Amide* (IV; R = $[CH_2]_8$·CH:CH_2).—*N*-Methylolundec-10-enoic amide, m. p. 77—78° (Jones and Pyman, *loc. cit.*) (3·8 g.), catechol (1·7 g.), and concentrated hydrochloric acid (2 c.c.) were kept for 48 hours in cold alcoholic solution (30 c.c.). After dilution with water the product was taken up in ether, washed with water, and extracted with dilute sodium hydroxide solution. The alkaline liquors were acidified, extracted with ether, and evaporated, and the residue was freed from catechol by trituration with water. The residual brown oil was taken up in ether and dried, and light petroleum (b. p. 40—60°) added until crystallisation commenced. The amide separated in small needles (0·1 g.), m. p. 85—86° (Found : C, 71·0; H, 9·1. Calc. for $C_{18}H_{27}O_3N$: C, 70·8; H, 8·9%) (Jones and Pyman, *loc. cit.*, give m. p. 70—74°), which are soluble in cold dilute sodium hydroxide solution, contain nitrogen, and give a deep green ferric test.

Allyl Protocatechuate (V; R = CH_2·CH:CH_2).—3 : 4-Carbonyldioxybenzoyl chloride (2 g.) and allyl alcohol (3 c.c.) were heated on the water-bath until hydrogen chloride evolution ceased (6 hours). Distillation yielded the crude ester carbonate as an oil (2·2 g.), b. p. 160—180°/1·2 mm., which partially solidified on cooling. The product was boiled with water (24 c.c.), and 2N-ammonia (28 c.c.) was added during 5 minutes. After boiling for 20 minutes the mixture was cooled, made alkaline with excess of ammonia, filtered, and treated suitably with ether, acid, and sodium bicarbonate to isolate the phenolic *ester* from neutral and acidic materials. The product crystallised from hot water (carbon) in prisms (0·5 g.), m. p. 108—110° (Found : C, 61·7; H, 5·4. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%), which gave a bright green ferric test.

Undec-10-*enyl Protocatechuate* (V; R = $[CH_2]_9$·CH:CH_2).—Undec-10-enyl alcohol (1·05 g.) (Grun and Wirth, *Ber.*, 1922, **55**, 2208) and 3 : 4-carbonyldioxybenzoyl chloride (1 g.) were heated at 100° for 3 hours. The mixture, which partially solidified on cooling, was heated for 15 minutes at 100° with N-ammonia (16 c.c.), cooled, and shaken with ether (20 c.c.) and 2N-sodium hydroxide (20 c.c.). The alkaline layer was acidified, extracted thrice with ether, the ethereal extract washed with aqueous sodium bicarbonate, dried, and the solvent removed. The residual *ester* crystallised from ligroin in prisms (1 g.), m. p. 83—85° with previous sintering at 75° (Found : C, 69·8; H, 8·3. $C_{18}H_{26}O_4$ requires C, 70·5; H, 8·6%), which gave a green ferric test.

2 : 3-(3′-*Hydroxy*-o-*phenylene*)*dioxydioxan* (VI; R = H).—2 : 3-Dichlorodioxan (20 c.c.; prepared by the method of

Kucera and Carpenter, *J. Amer. Chem. Soc.*, 1935, **57**, 2346), pyrogallol (12 g.), pyridine (28 c.c.), and benzene (60 c.c.) were heated on the water-bath for 16 hours. The mixture, which separated into two layers, was shaken with excess of sodium bicarbonate solution and twice extracted with benzene. The extract was dried, the solvent removed, and the dark residue distilled. The fraction of b. p. 150—170°/0·5 mm. was shaken with a mixture of water and ether; the ethereal layer was dried (Na_2SO_4), concentrated slightly, and ligroin added. On standing, the *substance* (VI; R = H) separated (6·9 g., m. p. 95—100°). Crystallisation from benzene–ligroin gave cubical crystals, m. p. 105—106° (Found: C, 57·1; H, 5·1. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%).

Preparation of Ethers (VI; R = alkyl).—The phenol (VI; R = H) (2 g.), the alkyl bromide or iodide (4—5 c.c.), and powdered anhydrous potassium carbonate (2 g.) were refluxed in acetone (5 c.c.) for 20—48 hours. After addition of water, the *ether* (VI; R = alkyl) was isolated with ether, washed with dilute sodium hydroxide solution, and crystallised from ether–ligroin. With some of the higher ethers a distillation was advisable before crystallisation. The properties of the ethers are included in Table I; they gave a negative ferric test and in general were obtained in 80% yields.

TABLE I.

Substance.	M. p.	Solvent.	Found (%). C.	Found (%). H.	Formula.	Required (%). C.	Required (%). H.
2:3-(3′-*Ethoxy*-o-*phenylene*)*dioxydioxan*	87°	Ether	60·1	6·1	$C_{12}H_{14}O_5$	60·5	5·9
2:3-(3′-n-*Propoxy*-o-*phenylene*)*dioxydioxan* ...	72	Benzene–ligroin	62·0	6·7	$C_{13}H_{16}O_5$	61·9	6·4
2:3-(3′-n-*Butoxy*-o-*phenylene*)*dioxydioxan* ...	74	Ether–ligroin	63·7	7·1	$C_{14}H_{18}O_5$	63·2	6·8
2:3-(3′-n-*Amyloxy*-o-*phenylene*)*dioxydioxan*	40	Ether–ligroin	64·5	7·3	$C_{15}H_{20}O_5$	64·3	7·1
2:3-(3′-n-*Hexyloxy*-o-*phenylene*)*dioxydioxan*	76	Ether–ligroin	64·5	7·6	$C_{16}H_{22}O_5$	65·3	7·5
2:3-(3′-n-*Heptyloxy*-o-*phenylene*)*dioxydioxan*	54	Ether–ligroin	66·3	8·1	$C_{17}H_{24}O_5$	66·2	7·9
2:3-(3′-n-*Octyloxy*-o-*phenylene*)*dioxydioxan*...	75	Ether–ligroin	67·5	8·3	$C_{18}H_{26}O_5$	67·1	8·1
2:3-(3′-n-*Hexadecyloxy*-o-*phenylene*)*dioxydioxan*	87	Ether–ligroin	71·6	10·0	$C_{26}H_{42}O_5$	71·9	9·8
2:3-(3′-*Allyloxy*-o-*phenylene*)*dioxydioxan* ...	92	Ether–ligroin	63·0	6·0	$C_{13}H_{14}O_5$	62·4	5·6

TABLE II.

Substance.	M. p. *ex* ligroin.	Found (%). C.	Found (%). H.	Formula.	Required (%). C.	Required (%). H.	Vesicancy tests.
3-*Ethoxycatechol*	91—93°	62·2	6·5	$C_9H_{10}O_3$	62·3	6·5	E_1−; nil.
3-n-*Propoxycatechol*	90—91	64·5	7·3	$C_{9}H_{12}O_3$	64·3	7·2	E_1−; E_1−; E_4.
3-n-*Butoxycatechol*	50—51	66·1	7·9	$C_{10}H_{14}O_3$	65·9	7·8	E_1−; E_1−; E_4.
3-n-*Amyloxycatechol*	59—60	67·3	8·4	$C_{11}H_{16}O_3$	67·4	8·2	E_1−; nil.

Preparation of 3-Alkoxycatechols.—The ether (VI; R = alkyl) (1 g.), urea (1 g.), acetic acid (5 c.c.), concentrated hydrochloric acid (8 c.c.), and water (2 c.c.) were refluxed for 6 hours. After dilution with water, the product was extracted with ether and the extract washed with sodium bicarbonate solution. The phenol was removed in 2% sodium hydroxide solution and recovered by acidification and ether extraction. The residue from the dried extract was purified either by distillation at 0·5 mm. or by crystallisation from ligroin. Yields of 30—35% were obtained with the 3-amyloxy- and lower ethers. The hydrolysis of the higher ethers was extremely slow; yields were very small and the products were oils, which were devoid of vesicant properties. The properties of the solid *3-alkoxycatechols* are given in table II: the oily higher members, like the crystalline lower members, were soluble in sodium hydroxide and with ferric chloride gave greenish-blue colorations which gradually became brown.

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THE UNIVERSITY, SHEFFIELD. [*Received, March 30th*, 1946.]

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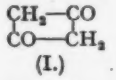
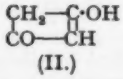
217. *The Structure of Dimeric Keten: Infra-red Measurements.*

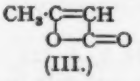
By D. H. WHIFFEN and H. W. THOMPSON.

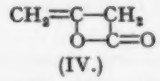
The infra-red spectrum of dimeric keten has been measured between 2 and 15 μ and correlated with the Raman spectrum. The results have been considered in relation to the different possible structures which have been suggested for this compound. Although an unambiguous decision cannot be made, some of the structures which are plausible on other grounds can be excluded, and it seems that the substance must have one of two possible lactone formulæ or be a mixture of them.

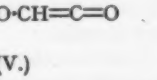
ALTHOUGH the dimer of keten is now an important synthetic reagent, its structure is still in doubt. Five possible formulæ, *viz.*, (I)—(V), have been suggested. Formula (I) was favoured by Rice and Roberts (*J. Amer. Chem. Soc.*, 1943, **65**, 1677) from results on the pyrolysis of diketen and examination of the products by experiments


(I.)


(II.)


(III.)


(IV.)

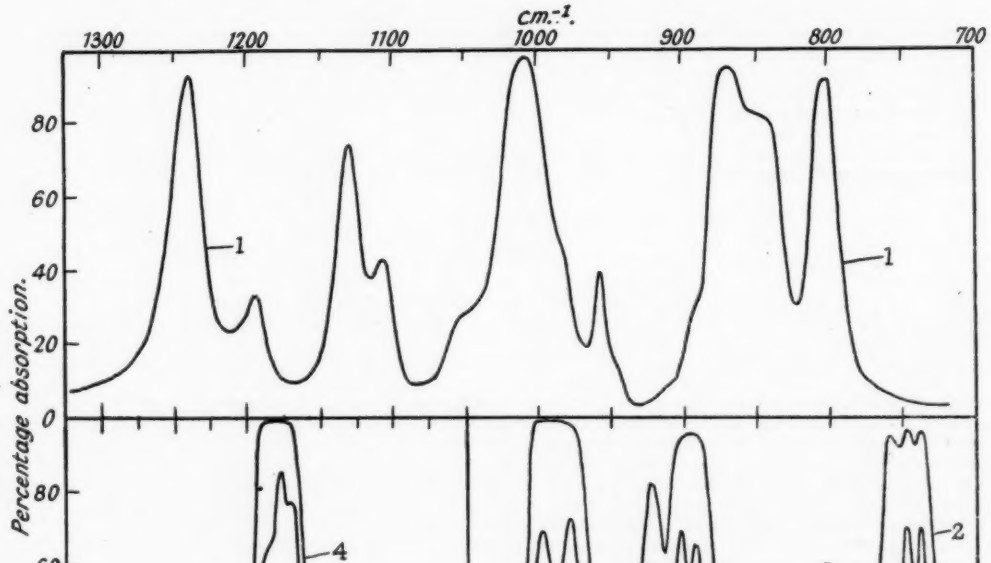

(V.)

on the " take-up " of metallic mirrors. Staudinger and Beretza (*Ber.*, 1909, **42**, 4908) and more recently Angus, Leckie, Le Fèvre, Le Fèvre, and Wassermann (*J.*, 1935, 1751) preferred formula (II), the last group of workers pointing out that the measured dipole moment is incompatible with (I), and that thermochemical data exclude a di-enolic form. From other pyrolytic experiments Hurd and his collaborators (*J. Amer. Chem. Soc.*, 1936, **58**, 962; 1939, **61**, 3355; 1940, **62**, 1147; 1941, **63**, 2174) have suggested that (III) or (V) must be the

correct formula. On the other hand, Boese (*Ind. Eng. Chem.*, 1940, **32**, 16) found that β-butyrolactone is formed by the catalytic reduction of dimeric keten, and argued that the formula must be (IV). Perhaps the only certain deduction from all these observations is that keten dimer cannot be exclusively (I).

The Raman spectrum was measured earlier by Angus, Leckie, Le Fèvre, Le Fèvre, and Wassermann (*loc. cit.*) both for the liquid and for solutions in carbon tetrachloride. Dr. Wassermann recently suggested to us that the infra-red absorption spectrum might throw further light on the problem, and kindly supplied us with two samples of the dimer. We have therefore measured the spectrum both of the liquid and of solutions in carbon disulphide, carbon tetrachloride, and chloroform, between 2 and 14 μ, using a single-beam recording spectrometer of high resolving power with rock-salt prism, and over the range 5—8 μ using a similar double-beam recording instrument. The great value of the latter instrument lies in its ability to obviate troubles due to the absorption by atmospheric water vapour near 6 μ; it will be described in detail elsewhere.

In the meantime the Raman spectrum has been re-measured by Taufen and Murray (*J. Amer. Chem. Soc.*, 1945, **67**, 754), who conclude that formulæ (I), (II), and (III) are impossible. Our present infra-red measurements, whilst also leading to no clear decision, serve to supplement the Raman spectra.



The dimeric keten was redistilled before use. Several samples were measured and gave the same spectrum. The absence of any of the strong bands of acetic anhydride showed that this possible impurity was absent; similarly no keten monomer could be detected, the spectrum of this substance having been measured also (Drayton and Thompson, to be published shortly).

The spectrum of the liquid is shown in the figure, and the positions of the absorption bands are listed in the table, together with the observed Raman intervals.

It may be noted that the relative intensity of the two infra-red bands at 1865 and 1895 appears to alter in different solvents. In carbon tetrachloride that at 1895 is the stronger, but in chloroform that at 1865. Similarly the bands at 1685 and 1705 vary in relative intensity in different solvents, and also shift slightly in wave-length.

Kohlrausch and Skrabal (*Proc. Ind. Acad. Sci.*, 1938, **8**, *A*, 424) have pointed out that the number of Raman intervals observed is greater than could arise if the molecule had the symmetrical structure (I). Another similar argument now strengthens this conclusion, since formula (I) has a centre of symmetry, and in this event there should be no " coincidences " between the active fundamentals, overtones or combination in the Raman spectrum on the one hand and the infra-red spectrum on the other. Inspection of the table shows that many such coincidences occur. This argument would lose its force if molecular distortion in the liquid led to a breakdown of the selection rules, but this does not seem to be so since the spectra of solutions in carbon

Positions of bands, in cm.$^{-1}$.

Infra-red.	Raman. T. and M.	Raman. K. and S.	Raman. A, L, F, F, and W.	Infra-red.	Raman. T. and M.	Raman. K. and S.	Raman. A, L, F, F, and W.
—	154 (44)	149 (4)	—	1417 m.	—	—	—
—	324 (8)	324 (2)	334	—	—	—	1547
—	444 (15)	438 (3)	450	1685 s.	1689 (10b)	1686 (1b)	—
—	504 (7)	501 (1)	—	1705 s.	—	—	1721
—	531 (20)	523 (3)	532	1745 s.	1760 (w)	—	—
—	—	—	613	—	1791 (w)	—	—
—	670 (100)	671 (8)	674	1865 s.	1859 (20)	1856 (3)	—
805 s.	803 (3)	800 (0)	—	1895 s.	1896 (14)	1891 (2)	1888
846 s.	840 (6)	844 (1)	—	—	—	—	1933
868 s.	870 (9)	864 (2)	865	2010 w.	—	—	—
893 ?	—	—	—	2040 w.	—	—	—
914 ?	—	—	—	2110 w.	—	—	—
946 ?	—	—	—	2230 w.	—	—	—
957 m.	951 (3)	951 (0)	—	2420 v.w.	—	—	—
986 w.	986 (10)	984 (2)	984	2480 v.w.	—	—	—
1009 s.	1017 (4)	1016 (1)	—	2560 w.	—	—	—
1055 w.	—	—	—	2660 v.w.	—	—	—
1106 m.	1104 (1)	1099 (1)	1104	2710 w.	—	—	—
1130 m.	—	—	—	2970 m.	2958 (61)	2966 (10b)	2962
1194 m.	—	—	1185	3010 m.	3019 (43)	3019 (10b)	3019
1239 s.	—	—	—	3082 w.	3072 w	—	—
—	—	—	1270	—	3127 (15)	3131 (4b)	3127
—	—	1313 (0)	—	—	—	3213 (1)	—
1375 m.	1374 (20)	1373 (3)	1374	3370 w.	—	—	—
1393 m.	—	—	—	3620 w.	—	—	—

disulphide are not appreciably different from that of the pure liquid. Thus there is evidence of all kinds against formula (I).

The infra-red spectrum provides definite evidence against formula (II). This structure has an enolic OH group, which should give rise to a band in the region of 3 μ, displaced to a greater or less extent from the normal position near 3600 cm.$^{-1}$ towards lower frequencies in consequence of molecular association. Dimeric keten has no band in this region which could indicate either the unassociated or the associated form, and it may be noted that the same argument applies to the Raman spectrum. The very weak bands in the infra-red spectrum in this region are much more reasonably interpreted as overtones and combinations. We have measured for purposes of comparison the absorption of *cyclo*pentanol as a liquid and also dissolved in carbon tetrachloride, and have found as expected the strong " association " band characteristic of the OH group. The concentration and path length were chosen so as to compare appropriately with those used in measuring the spectrum of dimeric keten and it is clear that no significant amount of hydroxylic structure can be present. We have also measured the spectrum of the enolic substance (VI) which shows the OH band.

$$\begin{matrix} CH(OH)=C\cdot CO_2Et \\ \qquad\quad | \\ \qquad\quad CH_2\cdot CO_2Et \end{matrix}$$
(VI.)

A decision between the remaining three formulæ is more difficult. The problem can be approached in three ways, by considering (1) the bands near 3000 cm.$^{-1}$, (2) the bands between 1500 and 2200 cm.$^{-1}$, and (3) the bands in the region below 1500 cm.$^{-1}$. The main bands in the region of 3000 cm.$^{-1}$ will be connected with stretching vibrations of C–H bonds, which have slightly different frequencies according to the particular structure of which the C–H bond forms a part. Intense infra-red bands between 1500 and 2200 cm.$^{-1}$ are usually attributed to vibrations which are largely controlled by the stretching of double bonds such as C=C, C=O, or C=N. The bands at frequencies below 1500 cm.$^{-1}$ are connected with vibrations of the skeleton, and are less easily correlated with specifically localised motions.

As regards (2), the region of the double-bond absorption, dimeric keten shows five fairly intense bands. Three of these, at 1685, 1865, and 1895 cm.$^{-1}$, have Raman analogues at 1689, 1859, and 1896, and a fourth at 1745 may be connected with the Raman interval 1760. We may now consider what frequencies would be expected in this region for each of the formulæ (III), (IV), and (V). Formulæ (III) and (IV) each have two double bonds, and will be expected to have two corresponding infra-red bands. Structure (V) has three double bonds, which will give three bands due to the stretching modes, but in the system >C=C=O, as with allene, >C=C=CH_2, one of the double-bond frequencies will lie lower, owing to interaction, and the other will be raised. In allene (Thompson and Harris, *Trans. Faraday Soc.*, 1944, **40**, 295) the two frequencies are 1069 and 1965 respectively, in keten at about 1130 and 2160, and in diphenylketen the higher frequency is at about 2130 cm.$^{-1}$. It is unlikely that the presence of the additional carbonyl group in dimeric keten if represented by (V) will raise the lower frequency just referred to by an amount sufficient to bring it above 1500 cm.$^{-1}$.

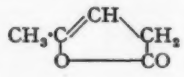
If therefore three or more of the five observed infra-red bands of dimeric keten in the range 1500—2000 cm.$^{-1}$ are due to double-bond fundamentals, no single formula is sufficient. We cannot decide whether three or more of the five bands are, in fact, due to fundamentals. They might be combinations, for example : 1865 ≈ (1009 + 846) or (1009 + 868), and 1895 ≈ (1239 + 670). None of the three structures involved has symmetry characteristics which might enable us to apply selection rules for the infra-red and Raman spectra.

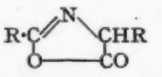
Hence the only further step possible is to compare the observed spectrum with those of other compounds

having a related structure. As regards (V), the acetylketen structure, it has already been stated that keten and diphenylketen have bands at 2160 and 2130 cm.$^{-1}$, and a frequency of about 2150 seems characteristic of the keten skeleton. The only question is whether the presence of the additional carbonyl group in the acetyl group, conjugated with the C=C linkage, can modify the frequencies of the >C=C=O skeleton so as to bring that at about 2150 down to 1895 or 1865. Although this effect is unpredictable, it does not seem likely. In mesityl oxide, $(CH_3)_2C{=}CH{\cdot}CO{\cdot}CH_3$, where the frequencies due to C=C and C=O are about 1625 and 1690, the conjugation has not much affected the " normal " values for those bonds. Hence the observed spectrum of dimeric keten seems against the presence of structure (V).

We therefore have to consider whether (III) or (IV), or a mixture of these, would give the spectrum found. Few compounds which are similar in structure to (III) or (IV) have been measured. The spectra of unsaturated compounds, ketones, and esters have shown that the stretching frequencies of C=C and C=O bonds can vary over wider limits than was previously supposed. It will become clear from the arguments given below that a clear decision between (III) and (IV) is impossible, and that a mixture of the two structures might satisfactorily explain the observed bands.

In saturated cyclic ketones the frequency of the carbonyl group depends upon the strain in the ring; thus in *cyclo*hexanone, *cyclo*pentanone, and *cyclo*butanone it lies at about 1710, 1740, and 1775 cm.$^{-1}$. The infra-red spectra of 5-membered lactones (Richards, to be published shortly) usually show a band due to the carbonyl group between 1740 and 1800 cm.$^{-1}$, and when a C=C link is included in the ring, the carbonyl frequency tends to lie at the higher end of this range. Thus, the lactone (VII) has the C=C frequency at 1675 cm.$^{-1}$ and the

(VII.) 

 (VIII.)

C=O frequency at 1800 cm.$^{-1}$. Similarly in simple oxazolones of the type (VIII), the carbonyl frequency lies at about 1800 cm.$^{-1}$. On passing from the 5- to the 4-membered ring as in (III) or (IV) the carbonyl frequency might be expected to rise slightly, but conjugation with the internal double bond as in (III) may diminish it. With dimeric keten, one of the bands at 1745, 1859, 1896 will be attributable to the C=O group. A decision between (III) and (IV) is clearly impossible.

As regards the C=C bond frequency, Taufen and Murray have drawn attention to the absence of a band between 1600 and 1640 cm.$^{-1}$ in the Raman spectrum which might have been attributed to this bond in a ring. Similarly there is no band in the range in the infra-red spectrum. In some 5-membered unsaturated lactones, however, such as (VII) (above), this frequency is as high as 1675 cm.$^{-1}$. Dimeric keten has a band at 1685. However, the decrease in the size of the ring in (III), as well as the conjugation, may be expected to lower this frequency somewhat. Hence formula (III) seems unlikely. If the correct formula is (IV), we might interpret the bands at 1745 or 1865, and 1685 as being due to the C=O and C=C stretching vibrations, and those at 1705, 1865, or 1745, 1895, and 1791 (Raman) as combinations.

This ambiguity between structures (III) and (IV), as well as the large number of strong bands in the " double bond " region, raises the question whether there are in reality two forms present. The close agreement between the spectra of different samples of dimeric keten, and the fairly close correspondence between the infra-red spectrum and the Raman spectrum measured by several independent laboratories, are against this hypothesis, unless the two forms are in equilibrium with each other. That some of the bands change in relative intensity with change of solvent is also noteworthy in this connexion. A change of the polar properties of the solvent might affect the band intensities with a single species, but if there were preferential interaction of some kind with one form of a pair, a similar result might be found.

As regards the region around 3 μ, the infra-red bands of dimeric keten at about 3010 and 3082 are paralleled by the Raman intervals 3019, 3072. The other infra-red band at about 2970 may be the analogue of the Raman interval 2960. Formulæ (III) and (IV) will each have four C–H stretching modes. Now C–H stretching vibration frequencies differ in magnitude according to the remainder of the molecule (Fox and Martin, *Proc. Roy. Soc.*, 1940, **175**, *A*, 208; Barnes *et al.*, *Ind. Eng. Chem. Anal.*, 1943, **15**, 659), but a useful generalisation is that for C–H bonds contiguous to an unsaturation, the frequencies are above 3000 cm.$^{-1}$, whilst in saturated compounds they are usually below 3000. In this respect the results probably favour (IV) rather than (III). The frequency at 3082 cannot be due to a vibration of the CH_3 group, is not likely to be due to the $\geqslant$CH group, but would agree with the group $=CH_2$. Moreover, the presence of the CH_3 group should give rise to a band between 2800 and 2900, and none is found. Hence the evidence seems to favour (IV).

As regards the bands below 1500 cm.$^{-1}$, we might expect to find a band near 1375 due to the symmetrical deformation of the CH_3 group, as found with many hydrocarbons, although it is now known that this band can be displaced considerably in some molecules as a result of neighbouring influences in the molecule. There is indeed a band at 1375 with dimeric keten, the low intensity of which may not be surprising if judged against those of the bands due to the more polar linkages. However, the methyl group should also give rise to a band in the region 1440—1460 cm.$^{-1}$, but none is found above 1417. In this connexion a suitable analogue to (III) might be methyl acetate (Thompson and Torkington, *J.*, 1945, 644). The observed spectrum seems therefore again to favour (IV) rather than (III), in which case the bunch of bands near 1400 cm.$^{-1}$ might be due to deformations of the group $=CH_2$ and the ring methylene group. Olefins containing the group $=CH_2$ give rise to an intense band near 890 cm.$^{-1}$ due to a deformational mode (Thompson and Torkington, *Proc. Roy. Soc.*,

1945, **184**, *A*, 13), which is somewhat displaced in non-hydrocarbon molecules. The strong band at 868 cm.$^{-1}$ with dimeric keten might be connected with this mode.

To summarise, therefore, the spectrum of dimeric keten suggests that it has the structure (III) or (IV), or is a mixture of both, and while much of the argument is tentative, the balance may favour formula (IV).

We are grateful to the Department of Scientific and Industrial Research for a Research Assistantship, and to the Government Grant Committee of the Royal Society for financial help in the purchase of apparatus. Our thanks are also due to Dr. Wassermann for suggesting the problem and for the gift of dimeric keten.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, January 25th*, 1946.]

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218. 2-*Butyne*-1 : 4-*diol. Part I. Reactions of the Hydroxyl Groups.*

By A. W. JOHNSON.

Esters, halides,* and ethers of 2-butyne-1 : 4-diol are described. 1 : 4-*Dibromo-2-butyne* and 1 : 4-*di-iodo-2-butyne* undergo anionotropic rearrangements on standing to the corresponding 2 : 3-dihalogeno-1 : 3-butadienes. 1-Ethoxy-1-buten-3-yne instead of the expected 1 : 4-diethoxy-2-butyne is obtained by the action of alcoholic sodium ethoxide on 1 : 4-*dichloro-2-butyne*. Substituted 1 : 4-diamino-2-butynes are prepared by the action of the appropriate amines on the 1 : 4-dihalogeno-2-butynes.* Malonic ester and ethylmagnesium bromide react normally with the 1 : 4-dihalogeno-2-butynes yielding 3-hexyne-1 : 1 : 6 : 6-tetracarboxylic ester and 4-octyne respectively. 2-Butyne-1 : 4-diol is converted to propargyl alcohol on heating with mild alkalis. Attempts to prepare 1 : 4-dicyano-2-butyne and to oxidise the carbinol groups of 2-butyne-1 : 4-diol have failed.

2-BUTYNE-1 : 4-DIOL was first obtained by Iotsitch (*J. Russ. Phys. Chem. Soc.*, 1906, **38**, 252) and later by Lespieau (*Ann. Chim.*, 1912, **27**, 137) and Dupont (*ibid.*, 1913, **30**, 485) by the interaction of acetylenedimagnesium bromide and formaldehyde or paraform. Lespieau (*ibid.*, 1914, **2**, 280; *Compt. rend.*, 1914, **158**, 707) has also obtained 2-butyne-1 : 4-diol by the action of zinc on 2 : 3-dibromo-2-butene-1 : 4-diol :

$$\left.\begin{array}{l} BrMgC{:}CMgBr + 2H{\cdot}CHO \\ CH_2(OH){\cdot}CBr{:}CBr{\cdot}CH_2{\cdot}OH \end{array}\right\} \xrightarrow[\text{hydrolysis}]{\text{after}} \xrightarrow[]{Zn} CH_2(OH){\cdot}C{:}C{\cdot}CH_2{\cdot}OH.$$

The compound was not further investigated until 1938; I.G. Farbenind. then claimed a new method for its preparation, by the interaction of acetylene with formaldehyde at an elevated temperature and pressure in the presence of a catalyst such as copper or silver acetylide on silica. The reaction can be carried out either as a continuous process (Swiss P. 220,204; Brit. Appl. 5810/40) or as a batch process (B.P. 508,062; General Aniline and Film Corp., U.S.P. 2,222,302). Later patents (U.S.P. 2,300,969) indicate that the presence of a cuprene inhibitor, *e.g.*, bismuth salts, is also desirable. Propargyl alcohol, a by-product in the manufacture of 2-butyne-1 : 4-diol, reacts with formaldehyde in the presence of a copper acetylide catalyst to give 2-butyne-1 : 4-diol (General Aniline and Film Corp., U.S.P. 2,238,471).†

Few of the reactions of 2-butyne-1 : 4-diol have been described in the literature. The possible reactions of this readily available intermediate may be divided into three types : (*a*) reactions involving the hydroxyl groups, (*b*) reactions involving the triple bond, and (*c*) reactions involving the hydroxyl groups and the triple bond. This paper is devoted to reactions of type (*a*). Reactions of types (*b*) and (*c*) will be described in Part II (following paper).

The following esters of 2-butyne-1 : 4-diol have been prepared : *diacetate*; *dibenzoate*; *bis*-(3 : 5-*dinitrobenzoate*); *bisphenylurethane*. 1 : 4-*Dichloro-2-butyne* was obtained in 90% yield by the action of thionyl chloride on the diol in the presence of pyridine; yields were poorer in benzene solution or using phosphorus trichloride, oxychloride, or pentachloride in benzene. 1 : 4-*Dibromo-2-butyne* was obtained in excellent yield by the action of phosphorus tribromide on a suspension of 2-butyne-1 : 4-diol in benzene, and 1 : 4-*di-iodo-2-butyne* was prepared from 1 : 4-dichloro-2-butyne by refluxing with a solution of potassium iodide in acetone. 2-Butyne-1 : 4-diol and thionyl bromide in pyridine solution yielded 1 : 2 : 2 : 4-*tetrabromobutane*, m. p. 72—73°, as a result of addition of hydrogen bromide to the triple bond. A liquid product described as possibly being 1 : 2 : 2 : 4-tetrabromobutane has been obtained by Demjanov and Dojarenko (*Ber.*, 1923, **56**, 2210) by the action of bromine on methylene*cyclo*propane. The action of piperidine on 1 : 2 : 2 : 4-tetrabromobutane gave a product, m. p. 98—99°, of undetermined structure.

1 : 4-Dibromo-2-butyne when freshly distilled showed a broad flat maximum at 2200—2250 A., $E^{1\%}_{1\,cm.}$ 186, $\epsilon_{max.}$ 3940. After exposure of the compound to air for five months this absorption rose to $E^{1\%}_{1\,cm.}$ 230, $\epsilon_{max.}$ 4900, indicating a slow irreversible change to 2 : 3-dibromo-1 : 3-butadiene. This change was accelerated by warming with benzoyl peroxide, the mixture becoming increasingly viscous and finally solidifying giving a pale yellow product, probably a polymer of dibromobutadiene, the bromine of which was only slightly attacked by

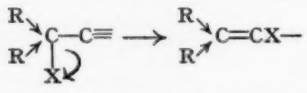
* Patent application pending.

† A review of the German work on 2-butyne-1 : 4-diol is contained in a translation of a paper by Reppe ("New Technical Applications of Acetylene," H.M. Stationery Office, 1946).

boiling sodium hydroxide. 1 : 4-Dibromo-2-butyne was largely unchanged by refluxing with iodine in acetone, or by heating for 4 hours in air; on heating at 170° for 1 hour in air it was converted into a black tar.

1 : 4-Di-iodo-2-butyne, even if freshly distilled, showed a maximum at 2400 A., $E^{1\%}_{1\,cm.}$ 324, $\epsilon_{max.}$ 9900, indicative of partial isomerisation to 2 : 3-di-iodo-1 : 3-butadiene. On exposure to air it rapidly precipitated a solid polymer, a change which could be retarded by addition of quinol and accelerated by warming with a little benzoyl peroxide. This polymer was insoluble in all common solvents, did not decolourise bromine in carbon tetrachloride, reduced neutral permanganate slowly, and was only slightly hydrolysed on boiling with 2N-sodium hydroxide.

1 : 4-Dichloro-2-butyne could not be induced to undergo this type of anionotropic rearrangement. There are several examples in the literature of analogous rearrangements of the dihalides of ditertiary acetylenic diols (Krestinsky *et al.*, *Ber.*, 1926, **59**, 1930; *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 1691; Zal'kind *et al.*, *ibid.*, 1926, **58**, 1044; 1927, **59**, 283; 1929, **61**, 803; 1930, **62**, 1022; Wieland and Kloss, *Annalen*, 1929, **470**, 201) which are more facile than the rearrangement of the acetylenic diprimary dihalides owing to the inductive effect of the additional alkyl groups which facilitate the separation of the anionic halogen atoms:



(X = halogen)

The structure of the 1 : 4-dihalogeno-2-butynes was proved by hydrolysis to 2-butyne-1 : 4-diol by refluxing with an aqueous suspension of calcium carbonate or silver oxide. The activity of the halogen atoms of the 1 : 4-dihalogeno-2-butynes was of the same order as that of the halogen atoms in the allyl halides and the 1 : 4-dihalogeno-2-butenes. As in the case of the allyl halides, a useful test for the 1 : 4-dihalogeno-2-butynes was the strongly exothermic reaction with piperidine or *cyclo*hexylamine, a reaction not shown by vinyl or alkyl halides (cf. Ziegler *et al.*, *Annalen*, 1942, **551**, 80).

In the presence of suitable diluents, 1 : 4-dihalogeno-2-butynes readily reacted with amines to yield the corresponding acetylenic diamines. The following have been prepared: 1 : 4-*diamino*- (hydrogenated over platinum to putrescine), 1 : 4-*di*(*methylamino*)-, 1 : 4-*di*(*butylamino*)-, 1 : 4-*di*(cyclo*hexylamino*)-, 1 : 4-*di*(*acetanilido*)-, 1 : 4-bis(dimethylamino)-, 1 : 4-*dipiperidino*-, and 1 : 4-*di*-(N-*methylanilino*)-2-*butyne*. No reaction occurred between 1 : 4-dichloro-2-butyne and diphenylamine. The manufacture of 1 : 4-bis(dimethylamino)-2-butyne has been described by I.G. Farbenind. (B.P. 510,904) by condensation of formaldehyde, dimethylamine, and acetylene over a copper acetylide catalyst. An attempt to prepare 1 : 4-dipiperidino-2-butyne by interaction of 2-butyne-1 : 4-diol and piperidine was unsuccessful, the reactants being recovered unchanged. It is therefore clear that the intermediate product in the direct synthesis from *sec.*-amine, formaldehyde, and acetylene is the hydroxy-methylamine and not 2-butyne-1 : 4-diol. With triethylamine, 1 : 4-dichloro-2-butyne formed 2-butyne-1 : 4-bis(triethylammonium chloride), characterised as the *dipicrate*. No pure product could be isolated from the corresponding reaction with pyridine. Attempts to hydrate 1 : 4-bis(dimethylamino)-2-butyne or 1 : 4-dipiperidino-2-butyne to the corresponding substituted 1 : 4-diamino-2-butanones by heating with Denigès's reagent (acid mercuric sulphate) were unsuccessful.

The aliphatic ethers of 2-butyne-1 : 4-diol can be obtained by the action of chloromethyl alkyl ethers on acetylenedimagnesium bromide (Gauthier, *Ann. Chim.*, 1909, **16**, 289; Lespieau, *ibid.*, 1912, **27**, 137; Dupont, *ibid.*, 1913, **30**, 485):

$$(\text{:CMgBr})_2 + 2CH_2Cl\cdot OR \longrightarrow (\text{:C}\cdot CH_2\cdot OR)_2 + 2MgClBr$$

1 : 4-Diethoxy-2-butyne has been prepared by this method. Kranzfelder and Vogt (*J. Amer. Chem. Soc.*, 1938, **60**, 1714) have prepared the dipropyl ether of 2-butyne-1 : 4-diol by the action of acetylenedimagnesium bromide on propylal:

$$2CH_2(OPr)_2 + (\text{:CMgBr})_2 \longrightarrow (\text{:C}\cdot CH_2\cdot OPr)_2$$

Attempts to prepare ethers directly from 2-butyne-1 : 4-diol by the action of the appropriate alcohol in the presence of sulphuric acid have failed.* The action of an alcoholic solution of sodium ethoxide on 1 : 4-dichloro-2-butyne yielded, not the expected 1 : 4-ethoxy-2-butyne, but 1-ethoxy-1-buten-3-yne, presumably with the intermediate formation of diacetylene (cf. G.P. 601,322).

$$CH_2Cl\cdot C\text{:}C\cdot CH_2Cl \xrightarrow{KOH} [HC\text{:}C\cdot C\text{:}CH] \xrightarrow{EtOH} HC\text{:}C\cdot CH\text{:}CH\cdot OEt.$$

The action of methyl alcoholic potassium hydroxide on 1 : 4-dibromo-2-butene did not proceed analogously, but yielded 1 : 4-*dimethoxy*-2-*butene*. Petrov (*J. Gen. Chem. Russia*, 1943, **13**, 108) has prepared 1 : 4-diethoxy-2-butene by this method and mentioned that a little 1-bromo-1 : 3-butadiene was obtained as a by-product, thus indicating that dehydrohalogenation occurs to a slight extent.†

The following aryl ethers of 2-butyne-1 : 4-diol have been prepared by the action of the sodium derivatives of the appropriate phenol on 1 : 4-dichloro-2-butyne: 1 : 4-*diphenoxy*-, 1 : 4-*di*-β-*naphthoxy*-, 1 : 4-*di*-(p-

* I.G. Farbenind. (G.P. 742,650) have since claimed the preparation of aliphatic ethers of 2-butyne-1 : 4-diol by the action of alkyl sulphates in the presence of aqueous alkali.

† Since this work was carried out, details of a German patent (I.G. Farbenind., G.P. 740,637) have appeared whereby diacetylene is prepared by the action of alkalis on 1 : 4-dichloro-2-butyne. This claim has been confirmed (author), and undoubtedly represents the most convenient laboratory method of preparation of diacetylene.

anilinophenoxy)-, and 1 : 4-*di*-(p-*acetamidophenoxy*)-2-*butyne*. 1 : 4-Diphenoxy-2-butyne, like the propargyl ethers (Tarbel, *Chem. Reviews*, 1940, **27**, 540), did not undergo a Claisen rearrangement to 1 : 4-di-(*o*-hydroxyphenyl)-2-butyne on heating.

1 : 4-Dichloro-2-butyne with ethyl sodiomalonate in toluene solution (alcohol is an unsatisfactory solvent) yielded a crude tetracarboxylic ester, hydrolysed to the corresponding acid which was then decarboxylated directly. The product was re-esterified with methyl alcohol and then fractionated to yield *methyl* 3-*hexyne*-1 : 6-*dicarboxylate* and *methyl* 3-*hexyne*-1 : 1 : 6-*tricarboxylate*. Hydrolysis of the former yielded 3-*hexyne*-1 : 6-*dicarboxylic acid* which gave suberic acid on hydrogenation with a platinum catalyst. The formation of the tricarboxylic acid in the decarboxylation of the tetracarboxylic acid can be avoided if the experiment is carried out on a small scale (approx. 5 g.). The structure of methyl 3-hexyne-1 : 1 : 6-tricarboxylate was proved by hydrogenation over platinum to *methyl hexane*-1 : 1 : 6-*tricarboxylate*, hydrolysis and decarboxylation of which gave suberic acid.

1 : 4-Dibromo-2-butyne with ethylmagnesium bromide yielded 4-octyne, the structure of which was proved by hydration to 4-octanone. Attempts to prepare 1 : 4-dicyano-2-butyne from the corresponding dihalides by the action of alkali metal cyanides or cuprous cyanide in various solvents were unsuccessful; either the dihalide was recovered unchanged, or extensive decomposition occurred. 1 : 4-Dichloro-2-butyne is largely unaffected by the action of potassium cyanide in boiling 2-ethoxyethanol, conditions which have been described by du Pont (U.S.P. 2,342,101) for the preparation of 1 : 4-dicyano-2-butene from the corresponding dichloride. 1 : 4-Dithiocyano-2-butyne was obtained by the action of an acetone solution of ammonium thiocyanate on 1 : 4-dichloro-2-butyne, but the crude product decomposed violently on attempted distillation. von Braun and Lemke (*Ber.*, 1922, **55**, 3536) have described a similar conversion of 1 : 4-dibromo-2-butene into the corresponding dithiocyanate. No reaction could be induced between 1 : 4-dichloro-2-butyne and magnesium in ether; with dibromobutyne, the reaction proceeded steadily at first but was eventually terminated by deposition of an insoluble substance on the magnesium. The solution gave a faint positive colour reaction for $-CH_2MgX$ (Gilman *et al.*, *J. Amer. Chem. Soc.*, 1925, **47**, 2002).

2-Butyne-1 : 4-diol has been converted into propargyl alcohol on heating with mild alkalis. Optimum conditions were obtained by heating the diol at 140° with 5% of its weight of potassium carbonate; a higher proportion of potassium carbonate caused the reaction to become too violent. Considerable tar formation accompanies the reaction and the yield of pure propargyl alcohol (estimated as the mercury derivative) is only 15—20%. 2-Butyne-1 : 4-diol is slowly decomposed on boiling with aqueous potassium hydroxide solutions to give formaldehyde (converted into potassium formate) and acetylene.

Attempts to oxidise the carbinol groups of the diol with chromic acid or with aluminium *iso*propoxide in the presence of acetone (cf. Heilbron, Johnson, and Jones, *J.*, 1939, 1560) were unsuccessful.

Reference is made in the experimental part to the vesicant and lachrymatory effects of some of the compounds described.

Experimental.

M. ps. are uncorrected. The microanalyses were carried out by Mr. E. S. Morton and the absorption spectra by Dr. F. R. Cropper.

2-Butyne-1 : 4-diol.—This was prepared by the interaction of acetylene and formaldehyde in the presence of a copper–silver acetylide on silica catalyst using bismuth oxyiodide as a cuprene inhibitor according to a modification of the method of I.G. Farbenind. (U.S.P. 2,300,969). The product, b. p. 145°/15 mm., m. p. 55°, crystallised in colourless plates from ethyl acetate. Small quantities are more conveniently crystallised from benzene. The diol is readily soluble in water, alcohols, and hot ethyl acetate; moderately soluble in cold ethyl acetate; sparingly soluble in benzene, chloroform, and ether; and almost insoluble in ligroin. It is odourless and non-explosive. There is some evidence that the solid has a slight vesicant action.

Esters of 2-Butyne-1 : 4-diol.—The *diacetate* was a colourless oil, b. p. 122—123°/10 mm., $n_D^{20°}$ 1·4611 (Found : C, 56·4; H, 6·2. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%). The *dibenzoate* formed prisms from methanol, m. p. 76—77° (Found : C, 73·3; H, 5·0. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%). The *bis*-(3 : 5-*dinitrobenzoate*) formed pale yellow plates from 2-ethoxyethanol, m. p. 189—191° (Found : C, 45·7; H, 2·4; N, 11·85. $C_{18}H_{10}O_{12}N_4$ requires C, 45·6; H, 2·1; N, 11·8%). The *bisphenylurethane* formed plates from benzene, m. p. 130—132° (Found : C, 66·2; H, 4·8; N, 8·9. $C_{18}H_{16}O_4N_2$ requires C, 66·7; H, 4·9; N, 8·6%).

1 : 4-*Dihalogeno-2-butynes.*—1 : 4-*Dichloro-2-butyne.* 2-Butyne-1 : 4-diol (100 g.; 1 mol.) was dissolved in dry pyridine (170 c.c.), and thionyl chloride (201 c.c.; 2·4 mols.) was added dropwise during 6 hours with stirring and cooling, the temperature being kept between 10° and 20°. The mixture was allowed to warm to room temperature, stirred overnight, and treated with crushed ice. The product was extracted with ether (3 × 200 c.c.), and the combined extracts were washed with sodium bicarbonate solution, dried, and fractionated to give 1 : 4-*dichloro-2-butyne* (118·7 g.; 83%) as a colourless oil, b. p. 68—69°/17 mm., 73°/24 mm., 165—166°/760 mm. (slight decomp.); $n_D^{20°}$ 1·5072; $d_4^{20°}$ 1·258. It exhibited no absorption of appreciable intensity in the range 2200—4000 A. (Found : C, 39·15; H, 3·4. $C_4H_4Cl_2$ requires C, 39·0; H, 3·3%). 1 : 4-Dichloro-2-butyne is a vesicant and a weak lachrymator. It was mainly unchanged (slight darkening) on refluxing with benzoyl peroxide, iodine, aluminium chloride, or zinc chloride.

1 : 4-*Dibromo-2-butyne.* 2-Butyne-1 : 4-diol (5 g.; 1 mol.) was suspended in benzene (40 c.c.) and phosphorus tribromide (13·7 g.; 2·4 mol.) added dropwise at room temperature with stirring; only a very slight temperature rise occurred and the stirring was continued overnight. Iced water was added and the mixture extracted with ether (3 × 50 c.c.); the combined extracts were washed with sodium bicarbonate solution, dried, and fractionated to give 1 : 4-*dibromo-2-butyne* (10·7 g.; 87%) as a pale yellow oil which darkened in air, b. p. 60°/0·07 mm., $n_D^{19°}$ 1·5927 (Found : Br, 75·9. $C_4H_4Br_2$ requires Br, 75·5%). 1 : 4-Dibromo-2-butyne is a powerful vesicant and lachrymator. On warming 1 : 4-dibromo-2-butyne with a small quantity of benzoyl peroxide the mixture became more viscous and finally solidified. The product was washed with hot ethanol and dried in a vacuum; it then formed a pale yellow solid (cf. Lespieau and Prévost, *Compt. rend.*, 1925, **180**, 675) giving a strong positive test for bromine. On heating, the polymer darkened at 120°, blackened at 170°, and completely decomposed at 200°.

1 : 2 : 2 : 4-*Tetrabromobutane.* 2-Butyne-1 : 4-diol (9 g.; 1 mol.) was dissolved in pyridine (18 c.c.; 1·1 mol.) and thionyl bromide (19 c.c.; 1·15 mol.; Hibbert and Pullman, *Inorg. Synth.*, 1939, **1**, 113) added dropwise (3 hours), the temperature of the reaction being kept at 15—20°. After 48 hours at room temperature, the mixture was decomposed with ice and extracted with ether (3 × 100 c.c.). The combined ethereal extracts were washed and dried and the solvent was removed; on cooling, the lachrymatory residue (15 g.) partly solidified and was crystallised from light petroleum (b. p. 40—60°) yielding 1 : 2 : 2 : 4-*tetrabromobutane* as colourless needles, m. p. 72—73° (Found: C, 13·1; H, 1·7; Br, 85·6. $C_4H_6Br_4$ requires C, 12·8; H, 1·6; Br, 85·6%).

1 : 4-*Di-iodo-2-butyne.* 1 : 4-Dichloro-2-butyne (5 g.) in dry acetone (50 c.c.) was refluxed overnight with powdered potassium iodide (20 g.). The black solution was poured into water and extracted with ether (3 × 100 c.c.); the combined extracts were washed with sodium thiosulphate solution until free from iodine, dried, and the solvent removed. Quinol (0·05 g.) was added and the residue distilled giving 1 : 4-*di-iodo-2-butyne* (6·5 g.; 52%) as a pale yellow oil, b. p. 70—72°/0·1 mm. (Found: C, 16·1; H, 1·45. $C_4H_4I_2$ requires C, 15·7; H, 1·3%). The product rapidly decolorised a solution of bromine in carbon tetrachloride and reduced neutral permanganate. In the absence of a stabilising agent (quinol), 1 : 4-di-iodo-2-butyne rapidly solidified; this change, which was complete after 6 hours at room temperature, was accelerated by warming, especially in the presence of a small quantity of benzoyl peroxide. In the presence of a small amount of quinol, rearrangement and polymerisation were not complete until after about 10 days. The solid polymer was washed with warm alcohol to remove iodine and dried in a vacuum (Found: C, 16·6; H, 2·1. $C_4H_4I_2$ requires C, 15·7; H, 1·3%). On heating, the polymer darkened at 150° and evolved iodine at a slightly higher temperature without melting.

Reactions of the 1 : 4-*Dihalogeno-2-butynes.*—(a) *Hydrolysis.* 1 : 4-Dichloro-2-butyne (1 g.) was refluxed overnight with a suspension of calcium carbonate (3 g.) in water (10 c.c.). The excess of calcium carbonate was separated and the filtrate evaporated to dryness on the steam-bath. The solid residue (3·8 g.) was distilled and the distillate, b. p. 140—150°/16 mm., which solidified on cooling was crystallised from ethyl acetate (carbon) giving 2-butyne-1 : 4-diol, m. p. 53—54°, alone and mixed with an authentic specimen. Hydrolysis was also effected by refluxing with an aqueous suspension of silver oxide, but the yield of 2-butyne-1 : 4-diol was lower.

(b) *Reaction with alcoholic sodium ethoxide.* 1 : 4-Dichloro-2-butyne (15 g.) was added to a solution of sodium ethoxide (from 6 g. of sodium) in ethanol (100 c.c.) and the mixture refluxed for 1 hour. The product was poured into water (600 c.c.) and extracted with ether (3 × 100 c.c.); the combined extracts were washed, dried, and distilled to give 1-ethoxy-1-buten-3-yne as a colourless oil (5·25 g.), b. p. 42°/15 mm., 71°/53 mm.; $n_D^{19°}$ 1·4759 (Viguier, *Compt. rend.*, 1912, **154**, 218; *Ann. Chim.*, 1913, **28**, 515, gives b. p. 29—33°/16 mm.; 126—130°/760 mm.; $n_D^{19.5°}$ 1·462. I.G. Farbenind., G.P. 601,822, give b. p. 46°/20 mm.) (Found: C, 74·7; H, 8·2. Calc. for C_6H_8O: C, 75·0; H, 8·3%). The product rapidly darkened in air and with an ammoniacal solution of silver nitrate gave an insoluble silver salt which exploded on rapid heating.

(c) *Reactions with alkali metal phenoxides.* The following general method was used. 1 : 4-Dichloro-2-butyne (1 mol.) and the appropriate phenol (2·5 mols.) in N/2-alcoholic potassium hydroxide (2·5 mols.) were refluxed overnight and the resulting ethers isolated either by direct filtration or by pouring into water and extraction with ether. The following 1 : 4-diaryloxy-2-butynes were obtained: *diphenoxy-*, colourless oil, b. p. 168°/3 mm. (Found: C, 80·1; H, 6·25. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%); *di-β-naphthoxy-*, m. p. 124—125° (from 80% aqueous 2-ethoxyethanol) (Found: C, 85·05; H, 5·3. $C_{24}H_{18}O_2$ requires C, 85·2; H, 5·3%); *di*-p-*anilinophenoxy-*, m. p. 88—89° (from light petroleum, b. p. 60—80°) (Found: C, 79·8; H, 5·2. $C_{28}H_{24}O_2N_2$ requires C, 80·0; H, 5·7%); *di*-p-*acetamidophenoxy-*, m. p. 218—220° (from ethanol) (Found: C, 67·85; H, 5·75; N, 7·85. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 8·0%).

(d) 1 : 4-*Diamino-2-butyne.* 1 : 4-Dichloro-2-butyne (5·12 g.) was stirred overnight with concentrated ammonia solution (*d* 0·880; 200 c.c.) at room temperature; the mixture rapidly became homogeneous. The excess of ammonia was removed on the steam-bath and the remaining solution acidified to Congo-red with hydrochloric acid. The acid solution was evaporated almost to dryness on the steam-bath, the residue made alkaline to Clayton-yellow with 10N-sodium hydroxide and extracted overnight with ether in a continuous extractor. Removal of the ether gave a dark brown oil which was distilled to give a main fraction (1·2 g.; 34%), b. p. 60—80°/11 mm., which on cooling solidified to a colourless crystalline mass of 1 : 4-diamino-2-butyne, m. p. 42—46°. The base readily absorbed carbon dioxide from the atmosphere, and was soluble in water and alcohols. The *dipicrate* formed yellow needles from water, m. p. 230—232° (decomp., with darkening at 160° and blackening at 200°) (Found: C, 35·1; H, 2·9; N, 20·1. $C_{16}H_{14}O_{14}N_8$ requires C, 35·4; H, 2·6; N, 20·6%).

1 : 4-Diamino-2-butyne (1·0 g.) in water (5·0 c.c.) was hydrogenated over Adams's platinum catalyst (0·1 g.) until no more hydrogen was absorbed (20 hours). After removal of the catalyst the aqueous solution of putrescine was converted directly into derivatives. Dibenzoyl derivative, colourless plates from aqueous methanol, m. p. 176—177° (*lit.* 177°). Dipicrate, yellow plates from water, m. p. 256° (decomp.) (*lit.* m. p. 250—255°). Attempts to prepare 1 : 4-diamino-2-butyne from 1 : 4-dichloro-2-butyne by the action of alcoholic ammonia yielded mainly a polymer, m. p. >330°, presumably $(NH{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CH_2)_n$. The action of liquid ammonia at −35° for five hours on 1 : 4-dichloro-2-butyne formed a small amount (25%) of the above polymer but the main portion (64%) was unchanged 1 : 4-dichloro-2-butyne.

(e) *Reactions with primary amines.* (i) 1 : 4-Dichloro-2-butyne (5 g.) was stirred with 22% aqueous solution of methylamine (290 g.) at room temperature for 16 hours; the solution was completely homogeneous after one hour. The product was treated similarly to the ammonia experiment (above) and the final alkaline solution extracted overnight with ether in a continuous extractor. Removal of solvent gave a brown oil which was dried over sodium and distilled to yield 1 : 4-*di*(*methylamino*)-2-*butyne*, b. p. 72°/20 mm. (1·5 g.), as a colourless oil (Found: N, 24·8. $C_6H_{12}N_2$ requires N, 25·0%). *Dipicrate*, yellow needles from water, m. p. 213—215° (decomp., with darkening at 180°) (Found: C, 38·2; H, 3·5; N, 19·0. $C_{18}H_{18}O_{14}N_8$ requires C, 37·9; H, 3·2; N, 19·6%).

(ii) 1 : 4-Dichloro-2-butyne (25 g.) and butylamine (86 c.c.) in benzene (240 c.c.) were refluxed for 3 hours. The product was cooled, treated with excess of 2N-sodium hydroxide, and the benzene layer washed and dried. After removal of the solvent the residue was distilled giving 1 : 4-*di*(*butylamino*)-2-*butyne* as a colourless liquid, b. p. 105—115°/0·2 mm., which very quickly darkened in air. A satisfactory analysis could not be obtained, probably because of this very rapid deterioration. *Dipicrate*, yellow needles from water, m. p. 206—207° (decomp.) (Found: C, 44·2; H, 4·7; N, 17·0. $C_{24}H_{30}N_8O_{14}$ requires C, 44·05; H, 4·6; N, 17·1%).

(iii) 1 : 4-Dichloro-2-butyne (5 g.) and *cyclo*hexylamine (17 g.) in benzene (25 c.c.) were heated under reflux for 3 hours. The benzene was then removed on the steam-bath and the residue distilled. The fraction, b. p. >150°/0·1 mm. (2·5 g.), solidified and was crystallised from light petroleum (b. p. 60—80°) giving 1 : 4-*di*(*cyclohexylamino*)-2-*butyne* as colourless needles, m. p. 83—84° (Found: C, 77·5; H, 10·9; N, 11·4. $C_{16}H_{28}N_2$ requires C, 77·4; H, 11·3; N, 11·3%).

(iv) 1 : 4-Dichloro-2-butyne (5·2 g.) and aniline (17 c.c.) in *n*-butanol (30 c.c.) were heated under reflux for 5 hours. The product was basified to Clayton-yellow with 2N-sodium hydroxide and distilled in steam to remove aniline and butanol. The residue was acidified to Congo-red with 2N-hydrochloric acid, clarified with carbon, cooled, and basified with 2N-sodium hydroxide; the base was then precipitated as a low-melting oil. This was extracted with ether (3 × 100 c.c.) and the combined ethereal extracts were washed and dried and the solvent was removed. The residue

of 1 : 4-dianilino-2-butyne was converted into the diacetyl derivative by boiling for 5 minutes with excess of acetic anhydride (20 c.c.). The product was poured into water and basified; the oil which separated rapidly solidified on cooling and was crystallised first from aqueous methanol and then from ligroin (b. p. 60—80°)–benzene yielding 1 : 4-*di*(*acetanilido*)-2-*butyne* as colourless needles, m. p. 99—100° (Found : C, 75·5; H, 6·1; N, 8·85. $C_{20}H_{20}O_2N_2$ requires C, 75·0: H. 6·25: N. 8·75%).

(f) *Reactions with secondary amines.* (i) 1 : 4-Dichloro-2-butyne (5·4 g.) in benzene (50 c.c.) was mixed with piperidine (14·9 g.). A vigorous reaction occurred and external cooling was necessary. After the initial reaction had subsided, the mixture was heated under reflux for 1 hour, cooled, and washed with excess of 2N-sodium hydroxide. The benzene layer was washed, dried, and distilled, giving 1 : 4-*dipiperidino*-2-*butyne* (4·8 g.; 57%) as a pale yellow oil, b. p. 124°/3 mm., $n_D^{19°}$ 1·5040 (Found : N, 12·6. $C_{14}H_{24}N_2$ requires N, 12·7%). *Dipicrate*, yellow needles from water, m. p. 204—205° (Found : C, 46·3; H, 4·9; N, 16·6. $C_{26}H_{30}O_{14}N_8$ requires C, 46·0; H, 4·4; N, 16·5%). 1 : 4-Dipiperidino-2-butyne was also obtained by the action of a benzene solution of piperidine on 1 : 4-dibromo-2-butyne or on freshly prepared 1 : 4-di-iodo-2-butyne, and was identified in each case as the dipicrate, m. p. 204—205°.

(ii) 1 : 4-Dichloro-2-butyne (10 g.) was added dropwise to a 21% aqueous solution of dimethylamine (100 g.) with stirring. Reaction occurred rapidly and the temperature rose to 50°. The mixture was stirred overnight at room temperature and then heated at 50° for 1 hour. After cooling, the solution was made alkaline to Clayton-yellow with 2N-sodium hydroxide and extracted overnight with ether in a continuous extractor. After removal of the ether, the residue was distilled and two fractions obtained : (*A*) b. p. 66°/54 mm., 54°/25 mm.; $n_D^{19°}$ 1·3888 (6·15 g.). (*B*) b. p. 92°/31 mm.; $n_D^{20°}$ 1·4561 (3·55 g.). Fraction (*B*) was 1 : 4-bis(dimethylamino)-2-butyne (I.G. Farbenind., B.P., 510,904, give b. p. 180°) and was converted into the *dipicrate*, yellow needles from water, m. p. 240—242° (decomp.) (Found : C, 40·1; H, 3·8; N, 18·55. $C_{20}H_{22}O_{14}N_8$ requires C, 40·1; H, 3·7; N, 18·7%). Fraction (*A*) was a constant-boiling mixture of water and 1 : 4-bis(dimethylamino)-2-butyne. It formed a dipicrate, m. p. 240—242°, identical with that obtained from the pure material.

(iii) 1 : 4-Dichloro-2-butyne (5 g.) and methylaniline (18 c.c.) in *n*-butanol (30 c.c.) were heated under reflux for 5 hours. The product was basified to Clayton-yellow with 2N-sodium hydroxide, and distilled in steam to remove methylaniline and *n*-butanol. The residue was acidified (Congo-red) with 2N-hydrochloric acid, clarified with carbon, cooled, and basified with 2N-sodium hydroxide. The colourless precipitate was collected, washed, and dried; m. p. 58—64° (8·0 g.). Crystallisation from light petroleum (b. p. 60—80°) gave 1 : 4-*di*-N-*methylanilino*-2-*butyne* as colourless needles, m. p. 63—64° (Found : C, 81·4; H, 7·4; N, 11·2. $C_{18}H_{20}N_2$ requires C, 81·8; H, 7·6; N, 10·6%).

(g) *Reactions with tertiary amines.* (i) A mixture of 1 : 4-dichloro-2-butyne (1 g.) and triethylamine (2·6 g.) in dry acetone (10 c.c.) was kept at room temperature overnight; a brown oil separated which slowly solidified to a grey crystalline mass of 2-butyne-1 : 4-bis(triethylammonium chloride). This was collected and washed with acetone; it was exceedingly deliquescent and was converted into the *dipicrate*, yellow plates from water, m. p. 229—231° (decomp., with previous darkening) (Found : C, 47·2; H, 5·3; N, 15·75. $C_{28}H_{40}O_{14}N_8$ requires C, 47·2; H, 5·6; N, 15·4%).

(ii) Interaction of 1 : 4-dichloro-2-butyne and pyridine in dry acetone yielded a black solid which could not be purified. It contained ionisable chlorine, and was very soluble in water and alcohol and sparingly soluble in acetone and petrol.

(h) *Reaction with ethyl malonate.* Ethyl malonate (215 c.c.) was added dropwise over ½ hour with stirring at 50° to powdered sodium (25 g.) in toluene (1200 c.c.) and then stirred at 50° for a further 4 hours. 1 : 4-Dichloro-2-butyne (50 g.) was added dropwise and the mixture heated at 80° with stirring overnight. The product was cooled and washed with excess of 2N-sulphuric acid and with water. Estimation of chloride ion in the combined aqueous washings indicated that the conversion of the 1 : 4-dichloro-2-butyne had been quantitative. The toluene layer was dried and the solvent removed under reduced pressure, leaving the crude tetracarboxylic ester which did not solidify on cooling. Potassium hydroxide solution (170 g. of potassium hydroxide in 950 c.c. of water) was added to the oil and the mixture heated on the steam-bath for 3 hours. The solution was acidified to Congo-red with concentrated hydrochloric acid and evaporated until a saturated solution was obtained which was cooled and extracted overnight with ether in a continuous extractor. Removal of the ether gave the crude tetracarboxylic acid which was divided into 3 portions, each of which was heated at 170—180° until evolution of carbon dioxide had ceased (1 hour). The combined products were dissolved in a mixture of methanol (500 c.c.) and sulphuric acid (20 c.c.) and refluxed for 3 hours, poured into water, and extracted with ether (3 × 200 c.c.). The combined extracts were washed, dried, and distilled, the following fractions being obtained. (*A*) b. p. 96°/0·2 mm. (5·7 g.), $n_D^{24°}$ 1·4600. (*B*) Intermediate : b. p. 97—130°/0·2 mm. (3·95 g.), $n_D^{19°}$ 1·4597. (*C*) b. p. 140—142°/0·1 mm. (37·6 g.), $n_D^{19°}$ 1·4625. (*D*) Residue. Fraction (*A*), *methyl* 3-*hexyne*-1 : 6-*dicarboxylate*, on cooling formed colourless crystals, m. p. 30—32° (Found : C, 60·3; H, 7·15. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%). Hydrolysis of the ester with aqueous potassium hydroxide gave 3-*hexyne*-1 : 6-*dicarboxylic acid* as colourless plates (from water), m. p. 208—209° (Found : C, 56·8; H, 5·9; equiv., 85·5. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%; equiv., 85·0). Complete hydrogenation of an aqueous solution of 3-hexyne-1 : 6-dicarboxylic acid in the presence of Adams's platinum catalyst at room temperature yielded suberic acid, m. p. alone and mixed with an authentic specimen 140—141°. Fraction (*C*), a colourless unsaturated viscous liquid, was *methyl* 3-*hexyne*-1 : 1 : 6-*tricarboxylate* (Found : C, 55·9; H, 6·5; equiv., 83. $C_{12}H_{16}O_6$ requires C, 56·2; H, 6·3%; equiv., 85·3). The tricarboxylic ester (4·5 g.) was completely hydrogenated in methanol (30 c.c.) in the presence of Adams's platinum catalyst. When no more hydrogen was absorbed (25 mins.), the catalyst was separated and the solvent removed. Distillation of the residue gave *methyl hexane*-1 : 1 : 6-*tricarboxylate* as a colourless oil, b. p. 154°/3 mm.; $n_D^{27°}$ 1·4426 (Found : C, 55·6; H, 7·65. $C_{12}H_{20}O_6$ requires C, 55·4; H, 7·7%). Hydrolysis of this ester with alcoholic potassium hydroxide yielded a brown oil (crude tricarboxylic acid) which was decarboxylated by heating at 180—190° for ½ hour until carbon dioxide evolution had ceased. On cooling, the product solidified and, after crystallisation from water, suberic acid, m. p. and mixed m. p. with an authentic specimen 140—141°, was identified.

Hydrolysis of methyl 3-hexyne-1 : 1 : 6-tricarboxylate with methyl alcoholic potassium hydroxide gave crude 3-hexyne-1 : 1 : 6-tricarboxylic acid. Attempts to decarboxylate this acid to 3-hexyne-1 : 6-dicarboxylic acid by heating alone at 190°, heating with copper bronze at 190°, or heating under reflux with acetic anhydride, were unsuccessful.

(i) *Reaction with ethylmagnesium bromide.* A solution of 1 : 4-dibromo-2-butyne (4 g.) in dry ether (10 c.c.) was added dropwise to an ethereal solution of ethylmagnesium bromide (from 1·4 g. of magnesium) during ½ hour with stirring. The pale yellow solution was refluxed overnight, cooled, and decomposed with excess of 2N-hydrochloric acid. The ethereal layer was removed and the aqueous layer extracted with ether (2 × 100 c.c.). The combined ethereal extracts were washed, dried, and distilled, giving a main fraction, b. p. 120—140° (1·2 g.) (Vaughn *et al.*, *J. Org. Chem.*, 1937, **2**, 1, give b. p. 130·5°/745 mm. for 4-octyne). This product was refluxed with Denigès's solution (20 c.c.) for 3 hours and the cooled product extracted with ether (3 × 50 c.c.), and the combined ethereal extracts were washed, dried, and distilled giving a main fraction, b. p. 50—70°/20 mm. (0·5 g.) (Tiffeneau and Deux, *Compt. rend.*, 1941, **212**, 105, give b. p. 70°/26 mm. for 4-octanone). The semicarbazone formed colourless plates from aqueous methanol, m. p. 98—99° alone and mixed with an authentic specimen (Bouveault and Locquin, *Bull. Soc. chim.*, 1906, **35**, 648, give m. p. 98—99°).

Propargyl Alcohol.—2-Butyne-1 : 4-diol (10 g.) was heated with potassium carbonate (0·5 g.) at 140—150° and the distillate collected in a cooled receiver. The yield of crude propargyl alcohol was 50—60% and of pure propargyl alcohol, 15—20% (estimated as the mercury derivative, m. p. 203—204°, colourless needles from 2-ethoxyethanol). On heating the diol with equal quantities of potassium carbonate, magnesium oxide, barium oxide, calcium carbide, calcium hydroxide, or sodium carbonate, the reaction was difficult to control and at well-defined temperatures violent decomposition occurred with formation of considerable amounts of acetylene. Below these temperatures, decomposition to propargyl alcohol and formaldehyde occurred smoothly.

1 : 4-*Dimethoxy-2-butene.*—1 : 4-Dibromo-2-butene (100 g.; Farmer, Lawrence, and Thorpe, *J.*, 1928, 729) was added to a solution of potassium hydroxide (58 g.) in methanol (750 c.c.) and the mixture refluxed for 1 hour. The precipitated potassium bromide was separated and most of the methanol removed from the filtrate by distillation through an 8-inch Widmer column. The residue was poured into water (500 c.c.) and extracted with ether (3 × 150 c.c.), and the combined ethereal extracts were washed, dried, and distilled to yield 1 : 4-*dimethoxy-2-butene* as a main fraction (42·5 g.), b. p. 77°/36 mm., $n_D^{20°}$ 1·4220 (Found: C, 63·0; H, 8·9. $C_6H_{10}O_2$ requires C, 63·2; H, 8·8%).

1 : 4-*Diethoxy-2-butyne.*—By the condensation of chloromethyl ethyl ether and acetylenedimagnesium bromide (Gauthier, *Ann. Chim.*, 1909, **16**, 289), 1 : 4-diethoxy-2-butyne was obtained in 70% yield as a colourless liquid, b. p. 82°/17 mm., 97—99°/38 mm.; $n_D^{20°}$ 1·4360 (Gauthier, *loc. cit.*, gives b. p. 179—180°/730 mm.; $n_D^{22°}$ 1·435), which rapidly darkened in air. This darkening could be delayed by the addition of a trace of quinol.

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Imperial Chemical Industries Limited,
Research Laboratories, Blackley, Manchester, 9.

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219. 2-*Butyne*-1 : 4-*diol. Part II. Reactions involving the Triple Bond.*

By A. W. Johnson.

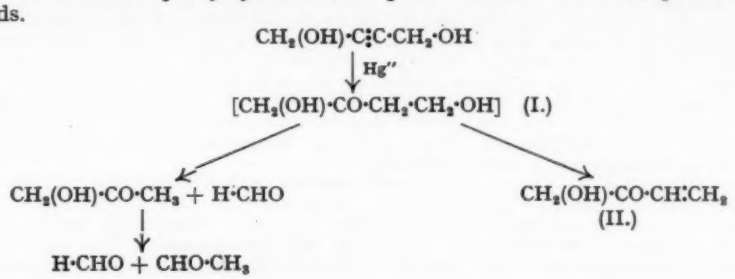
Hydrogenation of 2-butyne-1 : 4-diol yields either *cis*-2-butene-1 : 4-diol or butane-1 : 4-diol. Hydration in the presence of acid solutions of mercuric salts gives a variety of products derived from butane-1 : 4-diol-2-one. Addition of hydrogen chloride in the presence of cuprous chloride and ammonium chloride yields 2 : 2-*dichlorobutane*-1 : 4-*diol*, and addition of iodine yields 2 : 3-*di-iodo-2-butene*-1 : 4-*diol*. The action of hydrogen chloride at 100° or of 48% hydrobromic acid at room temperature gives the corresponding 2(3) : 4-dihalogeno-2-buten-1-ols.

The reactions of 2-butyne-1 : 4-diol involving the triple bond are mainly additions. Partial reduction to *cis*-2-butene-1 : 4-diol is known to be effected either by zinc and aqueous sodium hydroxide (I.G. Farbenind., B.P. 508,543) or by hydrogenation over partly poisoned catalysts (I.G. Farbenind., F.P. 853,148; General Aniline and Film Corp., U.S.P. 2,300,598). The *cis*-diol has now been prepared in excellent yield by hydrogenation at atmospheric pressure over 0·5% palladium–calcium carbonate or Raney nickel by taking advantage of the distinct change in the rate of hydrogenation after the absorption of one equivalent of hydrogen. This change of rate was not obtained with platinum catalysts in accordance with the observation of Lespieau (*Compt. rend.*, 1910, **150**, 1761). The identification of the ethylenic compound as the *cis*-isomer depended on the observation that its *dibenzoyl* derivative differed from that of the *trans*-diol, prepared by Prévost (*Compt. rend.*, 1926, **183**, 1292; 1928, **186**, 1209; *Ann. Chim.*, 1928, **10**, 400) by hydrolysis of *trans*-1 : 4-dibromo-2-butene.

Complete hydrogenation of 2-butyne-1 : 4-diol can be effected over a variety of catalysts, *e.g.*, nickel on pumice (I.G. Farbenind., U.S.P. 2,222,302; G.P. 721,004); copper (General Aniline and Film Corp., U.S.P. 2,335,795); platinum (Lespieau, *loc. cit.*); nickel, cobalt, copper, or silver (I.G. Farbenind., B.P. 508,944; U.S.P. 2,319,707). Butane-1 : 4-diol has also been obtained by hydrogenation of succinic ester (*inter al.*, Muller, *Monatsh.*, 1928, **49**, 28) and by hydrolysis of 1 : 4-diacetoxybutane (derived from tetrahydrofuran) by calcium oxide (Bennett and Heathcote, *J.*, 1929, 268). It has been shown that a more convenient method of hydrolysis of 1 : 4-diacetoxybutane is by the action of concentrated hydrochloric acid, but this method is unsatisfactory on a large scale. Hydrogenation of 2-butyne-1 : 4-diol over Raney nickel at elevated pressure has been repeated and this is undoubtedly the best laboratory method for preparing butane-1 : 4-diol which is an important industrial intermediate; dehydration yields tetrahydrofuran or 1 : 3-butadiene and halogenation yields the 1 : 4-dihalogenobutanes which may be converted into 1 : 4-dicyanobutane by the action of sodium cyanide (General Aniline and Film Corp., U.S.P. 2,222,302).

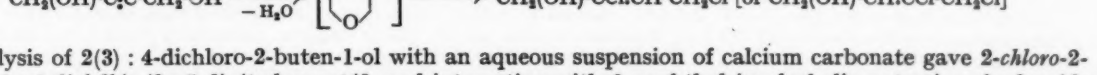
The hydration of the triple bond of 2-butyne-1 : 4-diol was first attempted by Dupont (*Ann. Chim.*, 1913, **30**, 485) with Denigès's solution (acid mercuric sulphate) but no product was isolated and the reagent was reduced to metallic mercury. The probable primary product of this hydration, butane-1 : 4-diol-2-one (I), has been reported to be unstable by Charlton and Kenner (*J.*, 1932, 750) who were unable to isolate the ketone or the corresponding oxime, but succeeded in isolating the phenylosazone. Although a neutral solution of mercuric chloride was reduced to mercurous chloride on warming with 2-butyne-1 : 4-diol, it has been found that, when Denigès's solution was used below 25°, acetaldehyde and formaldehyde could be isolated from the product as the corresponding 2 : 4-dinitrophenylhydrazones. Acetol, as the 3 : 5-*dinitrobenzoate*, and a ketone as its yellow 2 : 4-dinitrophenylhydrazone, $C_{10}H_{10}O_5N_4$, m. p. 111—115°, were also obtained. When the reaction mixture was warmed for a short time at 100°, a further product, probably 3-buten-1-ol-2-one (II),

was isolated as its red 2 : 4-*dinitrophenylhydrazone*, m. p. 232—234°. All these products were obtained in only very small yields.



Since the above work was carried out, Lozach (*Bull. Soc. chim.*, **1944**, **11**, 514) has reported that hydration of 2-butyne-1 : 4-diol in the presence of aqueous mercuric sulphate gives a polymeric substance probably formed by dehydration of (I) to (II) followed by polymerisation by sulphuric acid formed by hydrolysis of the mercuric sulphate. In boiling acetic acid in the presence of mercuric acetate, the diacetate of 2-butyne-1 : 4-diol was converted into 1 : 4-diacetoxy-2-butanone and 1-acetoxy-3-buten-2-one.

Hydrogen chloride has been added to 2-butyne-1 : 4-diol in the presence of cuprous chloride and ammonium chloride to yield 2 : 2-*dichlorobutane*-1 : 4-*diol*. The action of gaseous hydrogen chloride on 2-butyne-1 : 4-diol at 100° gave a small amount of 1 : 4-dichloro-2-butyne (Part I, preceding paper) together with 2(3) : 4-*dichloro*-2-*buten*-1-*ol* (*phenylurethane*). The mechanism of this reaction is uncertain but it is possible that 3-chloro-2 : 5-dihydrofuran is an intermediate.



Hydrolysis of 2(3) : 4-dichloro-2-buten-1-ol with an aqueous suspension of calcium carbonate gave 2-*chloro*-2-*butene*-1 : 4-*diol* [*bis*-(3 : 5-*dinitrobenzoate*)], and interaction with β-naphthol in alcoholic potassium hydroxide gave 2(3)-*chloro*-4-β-*naphthoxy*-2-*buten*-1-*ol*.

On dissolving 2-butyne-1 : 4-diol in 48% hydrobromic acid and keeping at room temperature for several days, the principal product was 2(3) : 4-*dibromo*-2-*buten*-1-*ol* which on treatment with β-naphthol in alcoholic alkali gave 2(3)-*bromo*-4-β-*naphthoxy*-2-*buten*-1-*ol*.

On warming 2-butyne-1 : 4-diol with a solution of iodine in aqueous potassium iodide, 2 : 3-*di-iodo*-2-*butene*-1 : 4-*diol* was formed; the dibromo-analogue was readily obtained by adding bromine to a benzene suspension of 2-butyne-1 : 4-diol (Lespieau, *Ann. Chim.*, **1912**, **27**, 137; **1914**, **2**, 280; *Compt. rend.*, **1914**, **158**, 707). No definite product was isolated from the action of chlorine on 2-butyne-1 : 4-diol, a reaction which is known to be complex with 2 : 5-dimethyl-3-hexyne-2 : 5-diol (Hennion and Wolf, *J. Amer. Chem. Soc.*, 1940, **62**, 1368). An attempt to prepare 2 : 3-dichloro-2-butene-1 : 4-diol from the dibromo-analogue by heating with an alcoholic solution of mercuric chloride also yielded a complex mixture of products.

It was not possible to add aniline to the triple bond of 2-butyne-1 : 4-diol; in the presence of mercuric chloride the diol was largely unchanged, and with sulphuric acid and mercuric sulphate hydration of the triple bond occurred. An attempted addition of hydroxylamine also failed. Addition products of certain amino-anthraquinones and 2-butyne-1 : 4-diol have been claimed (I.G. Farbenind., F.P. 828,581/50,208).

No Diels–Alder adduct of 2-butyne-1 : 4-diol and *cyclo*pentadiene could be obtained under the conditions recommended for the addition of 2-butene-1 : 4-diol, *viz.*, heating at 180° in an autoclave for 7 hours (I.G. Farbenind., F.P. 857,937). Acetylenic compounds are known to be often more reluctant than the corresponding ethylenic compounds to undergo Diels–Alder additions (Johnson, *J.*, 1945, 715). No formation of pyrazole derivatives was observed on allowing 2-butyne-1 : 4-diol to stand for two weeks in contact with excess of diazomethane in acetone.

Other reactions of 2-butyne-1 : 4-diol reported in the literature include addition of sodium hydrogen sulphite to give sodium butane-1 : 4-diol-2 : 3-disulphonate (I.G. Farbenind., F.P. 858,185); conversion into 4-hydroxybutaldehyde by passing an aqueous solution over a palladium–pumice catalyst at 105° in an atmosphere of hydrogen (I.G. Farbenind., U.S.P. 2,333,216); formation of pyrroles by passing the diol with ammonia or a primary amine over a heated catalyst (I.G. Farbenind., G.P. 701,825); and catalytic oxidation to maleic anhydride (I.G. Farbenind., F.P. 721,763/49,921).

Experimental.

M. ps. are uncorrected. Micro-analyses were carried out by Mr. E. S. Morton.

Hydrogenation.—(a) 2-*Butene*-1 : 4-*diol*. 2-Butyne-1 : 4-diol (20 g.) was dissolved in methanol (350 c.c.) and hydrogenated in the presence of 0·5% palladium–calcium carbonate (2·0 g.). After 24 hours, one equivalent of hydrogen (5650 c.c.) had been absorbed. The catalyst was then separated and the filtrate distilled, giving *cis*-2-butene-1 : 4-diol as a colourless oil (15·7 g.; 77%), b. p. 134—135°/15 mm., $n_D^{25°}$ 1·4716 (General Aniline and Film Corp., U.S.P. 2,300,598, give b. p. 129—130°/13 mm. for *cis*-2-butene-1 : 4-diol). The *dibenzoate* formed prisms from aqueous methanol, m. p. 69—70° (Prévost and Lutz, *Compt. rend.*, 1934, **198**, 2264, give m. p. 101° for the dibenzoate of *trans*-2-butene-1 : 4-diol) (Found : C, 72·85; H, 5·45. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). The *bis*-(3 : 5-*dinitrobenzoate*) formed pale

yellow plates from 2-ethoxyethanol, m. p. 171—172° (Found: C, 45·1; H, 2·75; N, 12·3. $C_{18}H_{12}O_{12}N_4$ requires C, 45·4; H, 2·6; N, 11·75%).

(b) *Butane-1 : 4-diol.* (i) 2-Butyne-1 : 4-diol (250 g.) in methanol (300 c.c.) was rotated in an autoclave at 150 atmospheres hydrogen pressure at room temperature with Raney nickel (50 g.) (I.G. Farbenind., B.P. 508,944). The reaction was very rapid (30 mins.) and external cooling was required. After removal of the catalyst the product was distilled to give butane-1 : 4-diol (230 g.; 92%) as a colourless oil, b. p. 128—129°/23 mm.

(ii) 1 : 4-Diacetoxybutane (44 g.) (Paul, *Compt. rend.*, 1929, **208**, 587) in ethanol (25 c.c.) was refluxed with concentrated hydrochloric acid (12·5 c.c.) and the solvent then removed on the steam-bath. The residue was distilled giving butane-1 : 4-diol, b. p. 125—126°/20 mm. (16·6 g.; 73%). Repetition of this experiment on a larger scale gave lower yields owing to the formation of some tetrahydrofuran.

Hydration.—2-Butyne-1 : 4-diol (20 g.) was added with stirring during 30 minutes to Denigès's solution (50 c.c.) [prepared by dissolving mercuric oxide (5 g.) in hot 27% sulphuric acid (140 g.)] with ice cooling. The solution rapidly darkened and mercury was precipitated (cf. Dupont, *loc. cit.*). After being stirred for a further hour, the solution was heated for ½ hour on the steam-bath; some tar had then formed. The cooled product was extracted with ether overnight in a continuous extractor, and the extract dried and distilled. The main fraction, b. p. 100—150°/15 mm. (1·3 g.), warmed with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride, gave a 2 : 4-*dinitrophenylhydrazone* which was dried and purified by chromatography of a benzene solution on alumina. The product, isolated by removal of benzene from the eluate, was obtained as red needles (from ethyl acetate), m. p. 232—234° (Found: C, 45·6; H, 3·4. $C_{10}H_{10}O_5N_4$ requires C, 45·2; H, 3·75%). Light absorption: The 2 : 4-dinitrophenylhydrazone in chloroform showed a main maximum at 3950—4000 A., $\epsilon = 21{,}300$, indicating that the compound is a derivative of an $\alpha\beta$-unsaturated ketone (cf. Braude and Jones, *J.*, 1945, 498). The experiment was repeated but without heating the reaction product at 100°. The ether distillate had a strong odour of acetaldehyde and on shaking with excess of aqueous 2 : 4-dinitrophenylhydrazine hydrochloride yielded acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 145—146° (alone or mixed with an authentic specimen) and formaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 164—166° (alone or mixed with an authentic specimen), separated by crystallisation from alcohol. A portion of the crude residue from the ether distillation was treated with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride solution, and the precipitate separated, dried, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°) yielding a 2 : 4-*dinitrophenylhydrazone* as a yellow solid, m. p. 111—115° (Found: C, 45·5; H, 3·75. $C_{10}H_{10}O_5N_4$ requires C, 45·2; H, 3·75%).

Treatment of a further portion of the crude residue from the ether distillation with 3 : 5-dinitrobenzoyl chloride and pyridine gave a small quantity of *acetol* 3 : 5-*dinitrobenzoate*, m. p. 92—93°, slender needles from aqueous methanol (Found: C, 45·0; H, 3·35; *M* (micro), 284. $C_{10}H_8O_7N_2$ requires C, 44·7; H, 3·0%; *M*, 268).

Addition of Hydrogen Chloride.—2 : 2-*Dichlorobutane-1 : 4-diol.* 2-Butyne-1 : 4-diol (20 g.) was stirred with a mixture of concentrated hydrochloric acid (78 c.c.), cuprous chloride (10 g.), and ammonium chloride (4 g.) at room temperature for 4 days. Most of the excess of hydrochloric acid was removed by aeration, precipitated salts were separated, and the filtrate was distilled. The main fraction, 2 : 2-*dichlorobutane-1 : 4-diol* (7·4 g.; 20%), b. p. 145—160°/15 mm., solidified on cooling and crystallised from benzene as colourless needles, m. p. 80—81° (Found: C, 30·5; H, 4·1; Cl, 44·3. $C_4H_8O_2Cl_2$ requires C, 30·2; H, 3·8; Cl, 44·6%).

Addition of Halogens.—(a) 2 : 3-*Di-iodo-2-butene-1 : 4-diol.* 2-Butyne-1 : 4-diol (2 g.) was warmed on the steam-bath for ½ hour with a solution of iodine (6 g.) and potassium iodide (8 g.) in water (70 c.c.). The precipitate, 2 : 3-*di-iodo-2-butene-1 : 4-diol*, was separated and washed; it crystallised from water (500 c.c.) as short colourless rods, m. p. 179—181° (with liberation of iodine) (Found: C, 14·6; H, 2·1; I, 74·2. $C_4H_6O_2I_2$ requires C, 14·1; H, 1·8; I, 74·7%).

(b) 2 : 3-*Dibromo-2-butene-1 : 4-diol* (Lespieau, *Ann. Chim.*, 1914, **2**, 280). Colourless needles (from benzene), m. p. 116—117°.

(c) *Addition of chlorine to 2-butyne-1 : 4-diol.* 2-Butyne-1 : 4-diol (10·5 g.) was stirred with a solution of chlorine (8·6 g.) in carbon tetrachloride (20 c.c.), at 5—10° for 2 hours. A black oil formed on the surface of the carbon tetrachloride. This oil was separated by decantation, washed, and distilled, but proved to be a complex mixture of labile products each of which, on exposure to air, blackened within a few minutes. No definite compound was identified apart from a small quantity of unchanged 2-butyne-1 : 4-diol.

Action of Hydrogen Chloride.—(a) Dry hydrogen chloride was passed into a stirred solution of 2-butyne-1 : 4-diol (20 g.) and acetic acid (1 g.) at 100—110° for 4 hours. The black oily product was distilled and the following fractions collected: (*A*) up to 50°/20 mm. (1·5 g.) which separated into 2 layers the upper one of which was water. (*B*) B. p. 102—122°/15 mm. (17 g.). (*C*) Residue. Fraction (*A*) was extracted with ether (3 × 5 c.c.) and the combined extracts were washed and dried. Removal of the solvent gave 1 : 4-dichloro-2-butyne (Part I, preceding paper) (0·7 g.; 2·4%), identified by conversion into 1 : 4-dipiperidino-2-butyne and thence into the corresponding dipicrate, m. p. 198—201° (decomp.) alone and m. p. 201—202° (decomp.) on admixture with an authentic specimen. Fraction (*B*) was redistilled and yielded 2(3) : 4-*dichloro-2-buten-1-ol*, b. p. 106°/15 mm., $n_D^{20°}$ 1·5042, as a colourless oil, almost insoluble in water but soluble in the common organic solvents (Found: C, 34·4; H, 4·3; Cl, 50·0. $C_4H_6OCl_2$ requires C, 34·0; H, 4·3; Cl, 50·3%). The *phenylurethane* had m. p. 64—65° from light petroleum (b. p. 40—60°) (Found: C, 50·6; H, 4·3. $C_{11}H_{11}O_2NCl_2$ requires C, 50·8; H, 4·2%).

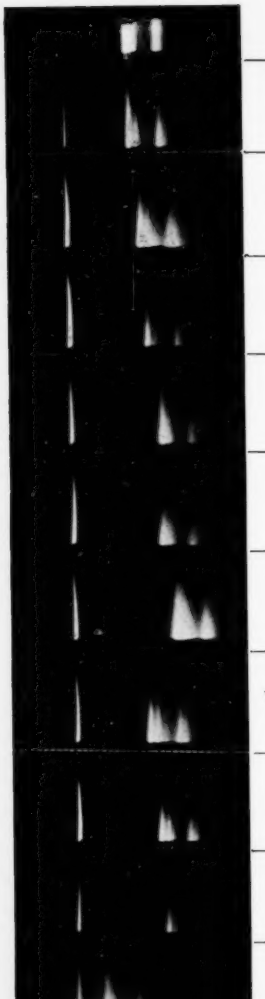
2(3) : 4-Dichloro-2-buten-1-ol (1·05 g.) was dissolved in a solution of β-naphthol (3 g.) in N/2-alcoholic potassium hydroxide (42 c.c.) and refluxed for 1 hour. The solution was poured into water (250 c.c.) and the precipitated 2(3)-*chloro*-4-β-*naphthoxy*-2-*buten*-1-*ol* collected, washed, and crystallised from aqueous ethanol; colourless plates, m. p. 95—96° (Found: C, 67·35; H, 5·1. $C_{14}H_{13}O_2Cl$ requires C, 67·6; H, 5·2%).

2(3) : 4-Dichloro-2-buten-1-ol (6 g.) was refluxed with a suspension of calcium carbonate (12 g.) in water (60 c.c.) for 2 hours. The excess of calcium carbonate was separated from the residue and the filtrate evaporated and distilled giving 2-*chloro*-2-*butene-1 : 4-diol* as a colourless water-soluble oil (1·9 g.), b. p. 141—142°/14 mm., $n_D^{20°}$ 1·4955 (Found: Cl, 28·5. $C_4H_7O_2Cl$ requires Cl, 28·9%). The *bis*-(3 : 5-*dinitrobenzoate*) formed pale yellow plates from 2-ethoxyethanol, m. p. 189—190° (Found: N, 10·9. $C_{18}H_{11}O_{12}N_4Cl$ requires N, 11·0%).

(b) 2-Butyne-1 : 4-diol was unaffected by a saturated aqueous solution of hydrogen chloride at 0° or by concentrated hydrochloric acid at room temperature. On refluxing with concentrated hydrochloric acid in the presence of zinc chloride, complete decomposition occurred with the formation of a black coke-like product.

Action of Hydrogen Bromide.—A solution of 2-butyne-1 : 4-diol (10 g.) in 48% hydrobromic acid (100 c.c.) was kept at room temperature for 7 days. The mixture, which rapidly darkened, was extracted with ether (3 × 100 c.c.) and the combined extracts were washed, dried, and distilled, and the following fractions collected; (*A*) b. p. 60°/0·05 mm. (14·6 g.), pale yellow oil; (*B*) b. p. 86°/0·05 mm. (2·6 g.), dark green oil. Fraction (*B*) has not been further investigated. Fraction (*A*) was 2(3) : 4-*dibromo*-2-*buten*-1-*ol* [Found: C, 21·2; H, 2·6; Br, 69·4; OH (Zerewitinoff), 6·3. $C_4H_6OBr_2$ requires C, 20·9; H, 2·6; Br, 69·55; OH, 7·4%]. On treatment of the product with piperidine a vigorous reaction occurred, showing the presence of the active bromine atom.

2(3) : 4-Dibromo-2-buten-1-ol (1 g.) was dissolved in a solution of β-naphthol (1·5 g.) in N/2-alcoholic potassium hydroxide (21 c.c.) and refluxed for 1 hour. The solution was poured into water (150 c.c.) and the precipitated



I. 3 : 4-*Benzpyrene* (*slit*).

II. 3 : 4-*Benzpyrene* (*moving wedge*).

III. 5-*Methoxy*-3 : 4-*benzpyrene*.

IV. 10-*Methoxy*-3 : 4-*benzpyrene*.

V. 8-*Methoxy*-3 : 4-*benzpyrene*.

VI. 5 : 10-*Dimethoxy*-3 : 4-*benzpyrene*.

VII. 5 : 8-*Dimethoxy*-3 : 4-*benzpyrene*.

VIII. 5-*Chloro*-3 : 4-*benzpyrene*.

IX. *Dichloro*-3 : 4-*benzpyrene*.

X. *Trichloro*-3 : 4-*benzpyrene*.

XI. *Chrysene*.

XII. 3-*Methoxychrysene*.

XIII. 4-*Methoxychrysene*.

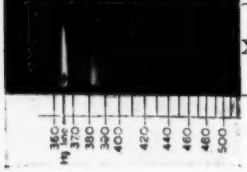
XIV. 2-*Methoxychrysene*.

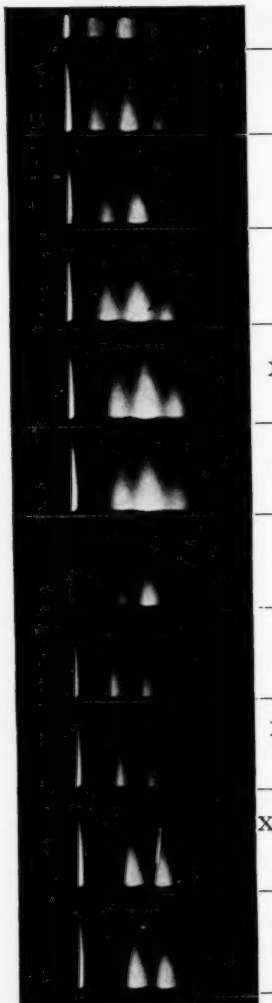
XV. 5-*Methoxychrysene*.

XVI. 6-*Methoxychrysene*.

XVII. 1-*Methoxychrysene*.

XVIII. 1 : 2-*Dimethoxychrysene*.





XIX. *Anthracene* (*slit*).

XX. *Anthracene* (*moving wedge*).

XXI. 2 : 3-*Dimethylanthracene*.

XXII. 2-*Methylanthracene*.

XXIII. 1 : 2-*Dimethylanthracene*.

XXIV. 1 : 3-*Dimethylanthracene*.

XXV. 1 : 4-*Dimethylanthracene*.

XXVI. 1 : 2-*Benzanthracene*.

XXVII. 4′-*Acetoxy*-1 : 2-*benzanthracene*.

XXVIII. 4′-*Methoxy*-1 : 2-*benzanthracene*.

XXIX. 4′-*Hydroxy*-1 : 2-*benzanthracene*.

XXX. 9 : 10-*Dimethoxy*-1 : 2-*benzanthracene*.

XXXI. 2 : 3 : 6 : 7-*Dibenzfluorene*.

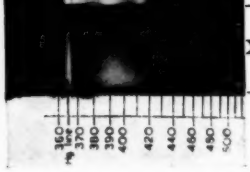
XXXII. 1 : 2 : 6 : 7-*Dibenzfluorene*.

XXXIII. 1 : 2 : 5 : 6-*Dibenzfluorene*.

XXXIV. 1 : 2 : 7 : 8-*Dibenzfluorene*.

XXXV. 1 : 2 : 3 : 4-*Dibenzfluorene*.

XXXVI. 3 : 4 : 5 : 6-*Dibenzfluorene*.



[*To face p.* 1017.

2(3)-*bromo*-4-β-*naphthoxy*-2-*buten*-1-*ol* collected and crystallised from 80% aqueous 2-ethoxyethanol (carbon clarification); colourless plates, m. p. 153—154° (Found : Br, 26·9. $C_{14}H_{13}O_2Br$ requires Br, 27·3%).

The author is greatly indebted to Mr. J. D. Rose for his advice throughout this work.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9. [*Received, March 6th*, 1946.]

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220. *Fluorescence Spectrography as an Aid in the Identification of Compounds.*

By I. BERENBLUM and (MISS) R. SCHOENTAL.

The fluorescence spectra of a group of polycyclic hydrocarbons, isomeric substitution products, and related compounds, were examined, using modifications in the standard technique, with the incorporation of a "moving wedge" near the slit of the spectrograph. The work provides additional data for judging the reliability of fluorescence spectrography in identifying certain types of compound.

FLUORESCENCE excited by ultra-violet light has wide applications, *e.g.*, in chromatography, quantitative analysis, and certain biological studies. The use of fluorescence spectrography by Mayneord played an important part in the isolation of 3 : 4-benzpyrene from tar (Cook, Hewett, and Hieger, *J.*, 1933, 395; Hieger, *Amer. J. Cancer*, 1937, **29**, 709), and has since been used in metabolic studies (Peacock, *Brit. J. Exp. Path.*, 1936, **17**, 164; Chalmers, *Biochem. J.*, 1938, **32**, 271; Berenblum *et al.*, *Cancer Res.*, 1943, **3**, 151; Doniach *et al.*, *Brit. J. Exp. Path.*, 1943, **24**, 1; and others). But its scope for wider use in the identification of compounds will depend on the accumulating evidence as to the specificity of fluorescence spectra in relation to molecular structure.

Hieger (*Biochem. J.*, 1930, **24**, 505) found characteristic banded fluorescence spectra a common feature among polycyclic hydrocarbons. The present use of a spectrograph of wider dispersion, and incorporation of a "moving wedge," provided improved facilities for assessing the characteristics of the band systems (compare I and II, or XIX and XX, Plate).

Characteristics of Fluorescence Spectra.—Though influenced by many factors (such as light source, optical system, plate sensitivity, and solvent), reproducible characteristic patterns for particular groups of compounds are obtainable. Under the conditions used in the present work, the spectra of anthracene and its methyl derivatives (XX—XXV) exhibited 4 single wide bands (the fourth too faint to be visible in the reproductions), of which the second band is the most intense, each band exhibiting maximal intensity at about its middle. Those of 3 : 4-benzpyrene and its derivatives (II—X) had very narrow bands, the first being most intense, with rapid rise and gradual fall in intensity of each band, the system displaying a "fluted" character (see Hieger, *loc. cit.*), *i.e.*, each major band being followed by one or two of weaker intensity. The spectra of 1 : 2-benzanthracene and its derivatives (XXVI—XXX) were similar to that of 3 : 4-benzpyrene, except for less tendency for duplication. Those of chrysene and its derivatives (XI—XVIII) resembled that of anthracene, but with weak bands in intermediate positions. The fluorescence spectrum of pyrene, consisting of multiple fine bands very close together (Hieger, *loc. cit.*; Mischer *et al.*, *Biochem. Z.*, 1936, **287**, 189), is an example of another characteristic pattern.

Derivatives with methyl, hydroxy-, methoxy-, acetoxy-, chloro-, and other substituents, have been examined. Though their introduction leads to a shift in the positions of the bands, to the longer wave-length, the patterns remained similar to those of the respective parent hydrocarbons. Less shift occurred with dimethyl substitution in the β- than in the α-positions of anthracene (compare XXI with XXV). Similarly, with the dibenzfluorenes, the bands of 2 : 3 : 6 : 7- (XXXI) were nearest to the shorter wave-length, while those of 3 : 4 : 5 : 6- (XXXVI) were furthest away. The chrysene series (XI—XVIII) illustrates the effect of methoxy-substitution in different positions of the molecule, the series being arranged, in the Plate, according to the degree of shift. Isomeric monomethoxybenzpyrenes (III—V) also show differences in the positions of the bands.

Different substituents in the same position of the molecule resulted in different degrees of shift, as seen in the 1 : 2-benzanthracene series (XXVI—XXIX), where less shift is seen with acetoxy- than with hydroxy- or methoxy-substitution. Mono-, di-, and tri-chlorobenzpyrenes (VIII—X) show progressive shift with multiple substitution; yet the position of substitution seems to be a dominant factor, since mono-substitution in some positions (*e.g.*, 8-methoxybenzpyrene, V) produces as much shift as di-substitution in other positions (*e.g.*, 5 : 10-dimethoxybenzpyrene, VI).

Intensity of Fluorescence.—This is strongly influenced by the set-up of the apparatus (light source, filter, dispersion of the spectrograph, size and position of tube, etc.), so that comparisons are valueless except under standard conditions. The nature of the solvent also affects fluorescence intensity (Miller and Baumann, *Cancer Res.*, 1943, **3**, 223; Weil-Malherbe, *ibid.*, 1944, **4**, 102), the position of the bands (Chalmers, *loc. cit.*; Sambursky and Wolfsohn, *Trans. Faraday Soc.*, 1940, **36**, 427), and their sharpness (definition being good in hexane, less good in benzene or ethanol, and poor in chlorine-containing solvents). Reduced intensity may result from oxygen-solubility in the solvent, leading to corresponding degrees of oxygen quenching (Bowen and Williams, *Trans. Faraday Soc.*, 1939, **35**, 765; Weil-Malherbe, *Cancer Res.*, 1944, **4**, 102), or from photo-oxidation, formation of polymers, or chemical interaction with the solvent, and may accordingly be affected

by the viscosity of the solvent, through influence on the collision of molecules (Bowen, " The Chemical Aspect of Light," 1946).

Liquid paraffin, having a low oxygen solubility, high viscosity, and no halogen or other disturbing group, has proved to be a highly suitable solvent for fluorescent work, exhibiting maximal intensity and good resolution of the bands (their positions corresponding to those in benzene, *i.e.*, slightly shifted to the longer wave-length as compared with those in hexane). All spectra in the Plate were obtained from solutions in liquid paraffin.

Semi-quantitative Estimations of Fluorescence Intensity.—The method of fluorimetric estimation by matching intensities of bands on photographic plates (Berenblum and Schoental, *Biochem. J.*, 1942, **36**, 86) was applied to the present series of compounds. Comparisons were made of the concentrations required to produce intensities comparable to that of a standard solution of 0·3 μg. of 3 : 4-benzpyrene per ml. of benzene (the values are obviously only approximate, in view of the different positions of the respective bands).

Hydrocarbons.—(*a*) 3 : 4-Benzpyrene and 1 : 2-benzpyrene were the most fluorescent of the series; (*b*) 20-methylcholanthrene, 1 : 2-benzanthracene, and anthracene required 15—30 times the concentration to produce comparable intensity; (*c*) 1 : 2 : 5 : 6-dibenzanthracene required about 200 times; and (*d*) chrysene, 3 : 4-benzphenanthrene, and pyrene required 2000 to more than 6000 times the concentration (the above estimations were in benzene; in other solvents, the ratios can be different).

Substitution Products.—The intensities of 5- and 8-methoxy-3 : 4-benzpyrene were about the same as that of 3 : 4-benzpyrene. With weaker fluorescing hydrocarbons, introduction of methoxy-groups actually increased the intensity of fluorescence, *e.g.*, 1- and 5-methoxychrysenes required 100—200 times lower concentration, 3-, 2-, and 6-methoxychrysenes required 30—40 times lower, and 4-methoxychrysene required 5 times lower concentration than chrysene to produce comparable intensities. With different substituents of 1 : 2-benzanthracene, the 4′-acetoxy- and the 9 : 10-dimethoxy-derivatives were only slightly more fluorescent than the parent hydrocarbon, while the 4′-hydroxy- and 4′-methoxy- were 4—5 times more intense. The finding that 1 : 2-dimethoxychrysene was about 20 times more fluorescent than chrysene, despite the close similarity in their spectra, is an example where quantitative values may be of help in identification.

Conclusions.—Differences in fluorescence spectra between an unknown and a reference substance can be taken as proof of non-identity. Similarity in spectrum, though not absolute proof of identity, represents a valuable addition to other methods of identification, and is specially useful when only minute amounts of material are available, or when still dealing with impure products. But as many factors influence fluorescence spectrography, comparisons must be made with reference to the particular set-up of apparatus, etc., rather than with published data of other workers.

Experimental.

The apparatus included a Bellingham & Stanley Intermediate Quartz Spectrograph (2000—8000 A. = about 15 cm.); Kodak I–F plates (sensitivity to about 6900 A.); Mercra Lamp (British Thomson-Houston Co. Ltd.); and Wood's glass filter. The lamp, with focusing quartz lens, was housed in a box with a small window, in front of which was the tube (thin-walled Monax, 7—8 mm. internal diameter) containing the test solution. Beyond the tube was the spectrograph, with its axis at about 110° to the beam of incident light. Slit: 0·05—0·2 mm.; exposures: 1—5 minutes, according to intensity of fluorescence.

The " moving wedge " consisted of a small elongated metal plate with a central opening, 4 cm. long, with one edge horizontal and the other cut according to a logarithmic scale. This was mechanically driven at a uniform rate (12 or 16 mm. per minute) perpendicular to the length of the slit, behind which it was situated.

Liquid paraffin (*d* 0·880—0·895) was used as solvent for investigation of characteristics of spectra by the " moving wedge " method. For quantitative estimations, benzene (and for some series, hexane) was used as solvent and diluent, 10 solutions (including one or more standards) being photographed on one plate. Exposures: 3 minutes without moving wedge.

The preparations of some of the compounds studied have previously been described (Berenblum and Schoental, *Cancer Res.*, 1943, **3**, 145, 686; Cook and Schoental, *J.*, 1945, 288), while the synthesis of 10-methoxy- and di- and trichloro-benzpyrenes, by Cook and Schoental, will be published elsewhere.

We are indebted to Professor E. L. Kennaway, F.R.S., for methylanthracenes and some other hydrocarbons, and to Professor J. W. Cook, F.R.S., for the dibenzfluorenes, 3 : 4-benzphenanthrene, etc. Our thanks are due to Mr. E. J. Bowen, F.R.S., and Professor F. Weigert for helpful criticism. We also thank Mr. H. W. Wheal for valuable technical assistance.

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221. *The Thermal Decomposition of* 2 : 3-*Dihydro-γ-pyran. A New Preparation of Acraldehyde.*

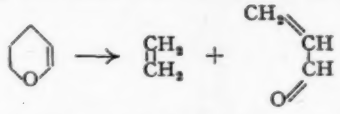
By John G. M. Bremner, David G. Jones, and Stanley Beaumont.

2 : 3-Dihydro-γ-pyran decomposes at 500—540° to give an 85% yield of acraldehyde and an 88% yield of ethylene. Addition of about 1% of methyl iodide does not increase the rate of formation of acraldehyde, but increases its rate of decomposition.

The yield of acraldehyde is not improved by use of an alumina–silica gel catalyst.

The material of the pyrolysis tube seems unimportant.

THIS paper describes a new and convenient method for the preparation of acraldehyde. The starting material



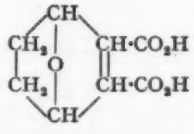
is 2 : 3-dihydro-γ-pyran (hereinafter referred to as dihydropyran) which is easily prepared by the dehydration of tetrahydrofurfuryl alcohol (*Org. Synth.*, **23**, 25; B.P. 547,334).

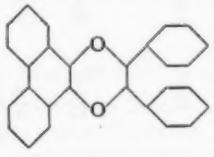
The thermal decomposition of dihydropyran at atmospheric pressure and 500—550° gives acraldehyde and ethylene (Nos. 1 and 2, Table I); some carbon monoxide, hydrogen, and high-boiling residues probably derived from acraldehyde are also formed. In the type of apparatus here described, 500 g. of dihydropyran/l. of reaction space/hr. can be decomposed to give about 300 g. of crude product from which 280 g. of pure acraldehyde can be obtained.

Details from other methods of preparing acraldehyde are given in Table II; advantages of this method are that no catalyst is required and that it can be operated continuously at atmospheric pressure to give excellent yields. The starting material is fairly readily available and is nearly all converted during one passage through the converter. The material of the pyrolysis tube seems to be unimportant as equally good results were obtained using tubes made of " Pyrex " glass, silica, mild steel, or 18/8 chrome–nickel steel.

This decomposition resembles those of the more complex heterocyclic compounds (I) and (II); thus, (I) breaks down when distilled at 11 mm. to give ethylene and furan-3 : 4-dicarboxylic acid (Alder and Reichert, *Ber.*, 1937, **70**, 1354) and (II) gives stilbene and phenanthraquinone when heated to 270° or treated with concentrated sulphuric acid at room temperature (Schönberg and Mustafa, *J.*, 1944, 387). The decomposition also resembles that of *cyclo*hexene and some substituted *cyclo*hexenes to give ethylene and butadiene or a sub-

(I.)





(II.)

stituted butadiene (Zelinsky, Mikhailov, and Arbuzov, *J. Gen. Chem. Russia*, 1934, **4**, 856; Rice, Ruoff, and Rodowskas, *J. Amer. Chem. Soc.*, 1938, **60**, 785; Rice and Murphy, *ibid.*, 1944, **66**, 785; Kuchler, *Trans. Faraday Soc.*, 1939, **35**, 874). In contrast with dihydropyran, however, the decomposition of *cyclo*hexene gives ethylene and butadiene in good yield only if carried out at low pressures under conditions in which 60% of the *cyclo*hexene is unchanged. A comparison of the conditions and results of the decompositions of *cyclo*hexene and dihydropyran is given in Table III. It is interesting to note that the heats of reaction calculated from Pauling's bond energy values seem to be low compared with those derived by using other methods.

While the union of ethylene and butadiene to give *cyclo*hexene has been carried out (Joshel and Butz, *J. Amer. Chem. Soc.*, 1941, **63**, 3350), no synthesis of dihydropyran from ethylene and acraldehyde has been reported.

Experiments were also carried out at temperatures in the range 475—550°; the results (Table IV) show a large variation in the proportion of carbon monoxide in the product, apparently independent of the amount of dihydropyran used up.

Many pyrolyses are known to proceed by a free-radical chain mechanism. Accordingly the influence of methyl iodide and of nitric oxide on the rate of production of acraldehyde was examined as methyl iodide is known to catalyse reactions involving free-radical chain mechanisms (Berents and Frost, *Compt. rend. Acad. Sci. U.R.S.S.*, 1939, **24**, 883; *Chem. Abs.*, 1940, 4058), and nitric oxide may have the opposite effect (Staveley and Hinshelwood, *J.*, 1937, 1568). The results of these experiments are given in Table V. In presence of methyl iodide, the total volume of gas produced has increased only slightly, while the proportion of carbon monoxide has increased greatly. This suggests that a reaction, apart from the decomposition of dihydropyran, is being catalysed which does proceed through a free-radical chain mechanism. This reaction is probably the decomposition of acraldehyde, which is known to be catalysed by iodine (Thompson and Frewing, *Trans. Faraday Soc.*, 1935, **31**, 1660), by ethylene oxide (Fletcher and Rollefson, *J. Amer. Chem. Soc.*, 1936, **58**, 2135), and by methyl iodide (Nos. 8 and 9, Table V). Nitric oxide has an effect similar to but less marked than that of methyl iodide. Now, the effect of nitric oxide on thermal decompositions is dependent on the concentration (Staveley and Hinshelwood, *Proc. Roy. Soc.*, 1939, *A*, **159**, 192), and in high concentration the effect may be to increase the rate of decomposition. The concentration of nitric oxide on the acraldehyde formed will naturally be high during the early stage of the reaction so that any inhibiting action may be masked.

The thermal decomposition of acraldehyde is a free-radical reaction propagated by a chain mechanism and it is likely that its rate of decomposition may be greatly affected by the presence of small amounts of impurities, say in the dihydropyran. This may explain the varying amounts of carbon monoxide found in the gaseous products of the decompositions of dihydropyran (Table IV), since under our conditions acraldehyde decomposes to give a gas consisting mostly of carbon monoxide (No. 8, Table V). It is concluded from these

TABLE I.

*Results of Thermal and Catalysed Decomposition of Dihydropyran.**

No.	Temp.	Dihydropyran fed (g.).	Rate, l. liq./l. pyrolysis space/hr.	Vol. of exit gas (l.) (S.T.P.) (N-free).	Analysis of exit gas (Orsat) (vol. %)					Liquid product (g.)	Liquid and gaseous product (g.)	Analysis of product (g.).		Dihydropyran converted (%).	Yield (%). Acraldehyde (*a*) and ethylene (*b*).
					CO_2.	C_nH_{2n}.	CO.	H_2.	C_nH_{2n+2}.						
1	540°	960	0·6	260	0·4	92·5	7·5	0	0	577	879	Acraldehyde	539	100	84·5 (*a*)
												Residue	36		87·5 (*b*)
2†	515	140	0·5	36·7	0·3	93·6	4·2	1·5	0·4	90	131·8	Acraldehyde (twice distilled, b. p. 52—54°)	65·6	97·1	72·5 (*a*)
															88·4 (*b*)
												Unchanged dihydropyran	4		
												Residue	8		
3‡	500	366	0·7	90·0	0·7	91·0	3·2	0·4	4·7	231·5	330·5	Acraldehyde	152	81·0	76·5 (*a*)
												Dihydropyran	69·5		96·9 (*b*)
												Residue	10		
4§	405	678	0·7	18·0	Analysis not reliable owing to large proportion of nitrogen present.					616 (containing 38 g. water)	616	Acraldehyde	8·4	45	4 (*a*)
												Dihydropyran	372		
												Mobile liquid residue	120		

* A silica converter tube was packed with glass wool for Run 1, silica chips for Run 2, and with alumina–silica gel catalyst (see Experimental) for Runs 3 and 4.
† A sample of the exit gas distilled in a low-temperature still gave the following results (% by vol.): CO, 5·2; H_2, 0·4; CH_4, 0·5%; C_2H_4, 92·5; C_2H_6, 0·1; C_3, 0·6; C_4, 0·7.
‡ A sample of the exit gas distilled in a low-temperature still showed that 99% of the unsaturated hydrocarbons was ethylene.
§ Poor weight recovery may be due to water retained in the catalyst from a dehydration reaction.

TABLE II.

Methods for Preparing Acraldehyde.

	Starting material.	Reagent or catalyst.	Temp.	Reaction products.	Yield (%).	Reference.
1	Glycerol	Na bisulphate	190—230°	$C_3H_4O + H_2O$	33—48	*Org. Synth.*, Vol. VI, p. 1
2	,,	Phosphates of Gp. I	400—420	,,	75—80	U.S.P. 1,916,743
3	Epichlorohydrin	$CaCO_3$	200	$C_3H_4O + HCl$	60	U.S.P. 2,106,347
4	Allyl alcohol	Cu	375	$C_3H_4O + H_2O$	78	F.P. 788,921
5	Allyl ether	Quartz	575	$C_3H_4O + CH_3{\cdot}CH{=}CH_2$	C_3H_4O, 86·5, C_3H_6, 95·4	U.S.P. 2,309,576
6	Propylene	$HgSO_4$ in H_2SO_4	80	$C_3H_4O + H_2O$	75% on $HgSO_4$	U.S.P. 2,197,258
7	Acetylene + formaldehyde	Metals, salts or oxides	180—300	C_3H_4O	—	U.S.P. 2,288,335
8*	Formaldehyde + acetaldehyde	Dehydration catalysts	250—325	$C_3H_4O + H_2O$	—	U.S.P. 2,245,582
9*	,, ,, ,,	Inert contact mass	200—600	,,	—	U.S.P. 2,246,037

* According to U.S.P. 2,277,887, it is important to prevent the vapours from the reaction described in Nos. 8 and 9 from coming into contact with Fe or Al; Cu, Ag, Ni, Cr, or ceramic materials may be used.

TABLE III.

Comparisons of Thermal Decompositions of Dihydropyran and cyclo*Hexene.*

	Dihydropyran.	*cyclo*Hexene.[1]
Moles used	1·0	1·0
Moles decomposed	1·0	0·39
Temperature	540°	790°
Pressure (mm.)	760	10—13
Contact time (secs.)	7·6	0·02
Moles feed/l. total reaction space/hr.	6·6	32·5
Yield (% theory on starting material destroyed) :		
Acraldehyde	84·5	—
Ethylene	87·5	93·0
Butadiene	—	92·2
Hydrogen	—	2·0
Approx. heats of reaction (kg. cals./mole) :		
(*a*) From heat of combustion [2]	—	43·1
(*b*) From bond energies [3]	17	45·5
Pauling [4]	8·2	31·1
(*c*) Group substitution method [5]	17·3	41·9

[1] Details of the pyrolysis from Rice, Ruoff, and Radowskas, *J. Amer. Chem. Soc.*, 1938, **60**, 955.
[2] Heat of formation of butadiene, Rossini, *Chem. Reviews*, 1940, **27**, 1; heat of combustion of *cyclo*hexene, Kharasch, *J. Res. Nat. Bur. Stand.*, 1929, **2**, 359; heat of combustion of ethylene, Kharasch and Knowles, *ibid.*, 1939, **19**, 339.
[3] No corrections for resonance energies of dihydropyran or acraldehyde as they are about equal (Kistiakowsky, *Chem. Reviews*, 1937, **20**, 181), resonance energy of butadiene taken as 3·5 kg.-cals. (calc. from hydrogenation heats, Kistiakowsky, *loc. cit.*).
[4] "Nature of the Chemical Bond," Pauling, Cornell University Press, 1944; assumptions of resonance energies in Ref. 3.
[5] Anderson, Beyer, and Watson, *Nat. Petroleum News*, 1944, **36**, *R*, 476.

TABLE IV.

Variation of Carbon Monoxide in Product in Thermal Decomposition of Dihydropyran.

(Pyrolysis carried out in silica tube packed with silica chips.)

Temp.	Space velocity, l. liquid/l. pyrolysis space/hr.	Analysis of exit gas after condensing system, % by vol. (Orsat). CO_2.	C_nH_{2n}.	CO.	H_2.	Dihydropyran converted (%).
475°	1·6	0·7	90·0	9·0	0·3	12·0
490	0·56	0·0	94·0	3·7	2·3	50·0
495	1·1	1·0	82·5	15·5	1·0	41·8
500	0·6	0·8	87·5	11·3	0·4	48·5
505	2·8	0·0	95·8	3·9	0·3	17·1
515	0·5	0·0	92·5	5·2	0·4	97
540	0·6	0·4	92·5	7·5	0	100

TABLE V.

Effect of Methyl Iodide and Nitric Oxide on the Pyrolysis of Dihydropyran and Acraldehyde.

(Pyrolysis carried out in a silica tube packed with silica chips as described in Experimental section. Temperature, 450°. Space velocity, 0·5 l. liquid/l. pyrolysis space/hr.)

No.	Feed.	Added material.	Moles gas/mole feed. H_2.	C_nH_{2n}.	CO.	Total.	Moles C_nH_{2n} / Moles CO
1	Dihydropyran	None	0·007	0·19	0·007	0·20	27·2
2	,,	,,	0·004	0·29	0·013	0·30	22·4
3	,,	1% CH_3I	—	0·27	0·047	0·32	5·7
4	,,	,,	0·001	0·20	0·030	0·23	6·6
5	,,	,,	0·002	0·27	0·070	0·34	3·8
6	,,	0·3% NO	0·010	0·22	0·014	0·24	15·7
7	,,	0·4% NO	0·002	0·23	0·023	0·25	10·0
8	Acraldehyde	None	—	—	—	0·01	—
9	,,	1% CH_3I	0·003	0·001	0·02	0·02	0·06

results that the thermal decomposition of dihydropyran does not take place to any extent through a chain mechanism involving free radicals.

The use of alumina–silica gel catalysts in the "cracking" of petroleum hydrocarbons has received considerable attention. Its effect may be to change completely the course of the reaction compared with the uncatalysed, thermal decomposition; thus, *cyclo*hexene passed over such a catalyst at 300° and at atmospheric pressure gave a 70% yield of methy *cyclo*pentenes (Bloch and Thomas, *J. Amer. Chem. Soc.*, 1944, **66**, 1589; cf. also Greensfelder and Voge, *Ind. Eng. Chem.*, 1945, **37**, 983). The results (Nos. 2 and 3, Table I) show that an alumina–silica gel catalyst had no effect in changing the course of the thermal decomposition of dihydropyran at 500°; at 400°, unidentified high-boiling products were formed. Some of the work described in this paper has formed the subject matter of B.P. 573,507.

Experimental.

The pyrolysis tube (110 cm. × 2 cm. i.d.) was contained in a vertical iron tube electrically heated by means of three separately controlled electrical windings. The temperatures in the annulus between the pyrolysis tube and the furnace wall were measured by two fixed thermocouples, while the temperatures inside the tube were measured by means of a moveable thermocouple in a glass or silica sheath passing down the axis of the tube. The volume of empty pyrolysis zone was 100 ml.; when packed with silica chips the free space was 53 ml. Dihydropyran was run into the top of the pyrolysis tube through a capillary tube; the rate was controlled by varying the pressure of nitrogen on a calibrated reservoir. The products were cooled by a water-cooled double surface condenser and the condensate caught in an ice-cooled catchpot containing some quinol to stabilise the acraldehyde. Uncondensed material then passed through a catchpot cooled in solid carbon dioxide–methanol and then through a rotary gas meter to the atmosphere. When only a small volume of gas was evolved, all the gas was collected in a large aspirator over acidified brine.

The decompositions were carried out in the following tubes: (1) silica tube packed with silica chips; (2) "Pyrex" glass tube packed with "Pyrex" glass cuts or glasswool; (3) "Pyrex" glass tube packed with 18/8 Cr–Ni steel turnings; (4) mild steel tube (unpacked); (5) 18/8 Cr–Ni steel tube packed with turnings of the same material; (6) silica tube packed with 100 ml. of alumina–silica gel catalyst.

Materials.—Tetrahydrofurfuryl alcohol was dehydrated to dihydropyran by the method described in B.P. 547,334. Acraldehyde was prepared from dihydropyran as described in this paper; it was stabilised with 0·1% of quinol and was redistilled before use. Nitric oxide was prepared from ferrous sulphate and sodium nitrite solution (Weil-Malherbe and Weiss, *J.*, 1944, 541); it was washed with 20% sodium hydroxide solution before use and was passed into the apparatus from a gas burette through a tube containing pellets of sodium hydroxide. Alumina–silica gel catalyst was prepared according to the method given in U.S.P. 2,270,090.

Analysis of Products.—The reaction products condensed in the catchpots were analysed by distillation at atmospheric pressure through a 3-inch column estimated to contain 6—7 theoretical plates. The uncondensed gas was analysed in an "Orsat" apparatus, and the gaseous products from two runs (Nos. 1 and 2, Table V) were analysed by distillation in a low-temperature still.

Properties of Acraldehyde from Thermal Decomposition (No. 1, Table I).—The properties of the twice distilled acraldehyde are compared in Table VI with the literature and calculated values.

Table VI.

Properties of Acraldehyde obtained by Thermal Decomposition.

Source.	B. p.	$d_4^{20°}$.	$n_D^{20°}$.	C (%).	H (%).	CHO (%).*
Thermal decomp.	52—54°	0·837	1·4025	64·2	7·2	52·5
Lit. or calc. for C_3H_4O	52·5	0·841	1·3997	64·3	7·1	51·78

* The analysis was done by Ripper's method, using potassium hydrogen sulphite ("Volumetric Analysis," Sutton, 1935, 12th Edn.); high results were obtained with the same sample using the method of oximation under pressure in presence of pyridine (59·5%, 60·4% CHO) (Smith and Bryant, *J. Amer. Chem. Soc.*, 1935, **57**, 57) or the normal sulphite method (61·0%, 61·6% CHO).

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222. *The Autoxidation of Methyl Oleate in Presence of Small Proportions of Methyl Linoleate.*

By F. D. Gunstone and T. P. Hilditch.

The autoxidation of methyl oleate is strongly accelerated, and the induction period much reduced, in presence of 1% of methyl linoleate at 20°, or of 0·2% of the ester at 50°; the oxidation of the methyl oleate is catalysed by hydroperoxides resulting from the union of oxygen with methyl linoleate.

The mechanism of addition of oxygen to systems such as $-CH_2\cdot CH{:}CH\cdot CH_2-$ and $-CH_2\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot CH_2-$ has been further considered. It is now suggested that oxygen molecules are primarily attached to an ethenoid bond, and not to an adjacent methylene group, hydroperoxide formation finally taking place with formation of a new ethenoid bond:

$$-CH{:}CH\cdot CH_2- \longrightarrow \overset{-CH\cdot CH\cdot CH_2-}{\underset{O-O}{\vdots\ \vdots}} \longrightarrow -CH(OOH)\cdot CH{:}CH-$$

It was shown (*J.*, 1945, 836) that the rates of autoxidation of methyl oleate, linoleate, and linolenate at 20° were in the approximate ratio 1 : 12 : *ca.* 25, and that, at 20° and 50°, methyl oleate exhibited prolonged "periods of induction" before steady addition of oxygen set in, whereas methyl linoleate and linolenate showed no measurable induction periods. The union of gaseous oxygen, at 20° and 50°, with methyl oleate to which very small proportions of methyl linoleate had been added has now been similarly studied by observation of the development of peroxide value (Figs. 1 and 2). At 20°, presence of 1% of methyl linoleate caused considerable reduction of the induction period, whilst with 2% and 5% of methyl linoleate the induction periods were still more reduced; after the induction periods, rapid absorption of oxygen proceeded in each instance at a steady rate over the ranges (usually to peroxide values of 400 or above) followed experimentally. At 50°, 1% of methyl linoleate caused great, and 0·5% or 0·2% of linoleate somewhat less, reduction of the induction period, the rate of subsequent increase in peroxide value again being rapid and almost linear in character:

	Oxidations at 20°.				Oxidations at 50°.			
Concn. of linoleate (%)	5	2	1	0	1	0·5	0·2	0
Induction period (hours)	85	185	320	800	75	100	120	210
Subsequent rate of increase of peroxide value (units per hour)	1·7	1·3	0·6	0·4	5·1	2·9	3·3	2·4

From these figures it is clear that the relatively slow autoxidation of the mono-ethenoid ester is powerfully catalysed by the presence of very small proportions of methyl linoleate, 0·2% of which is sufficient to cause marked acceleration of the union of oxygen with methyl oleate at 50°. The data definitely confirm the view, probably already widely held, that oxidative rancidity in edible fats is largely conditioned by linoleo-glycerides present rather than by oleo-glycerides, although the latter (as indeed is made plain by the above evidence) are also involved in its final development. Unfortunately, none of the natural materials employed in edible fats is free from linoleo-glycerides, whilst our present experiments prove that the presence of but small proportions of the latter provide the necessary catalyst for oxidative attack on the mono-ethenoid glycerides also present. (Mild hydrogenation of certain fats, *e.g.*, lard, increases their stability to oxygen owing to selective conversion of linoleo- into oleo- or *iso*oleo-glycerides; but for technical reasons this procedure is practicable only in a few restricted instances.)

FIG. 1.

Autoxidation of methyl oleate–methyl linoleate mixtures at room temperature (20°).

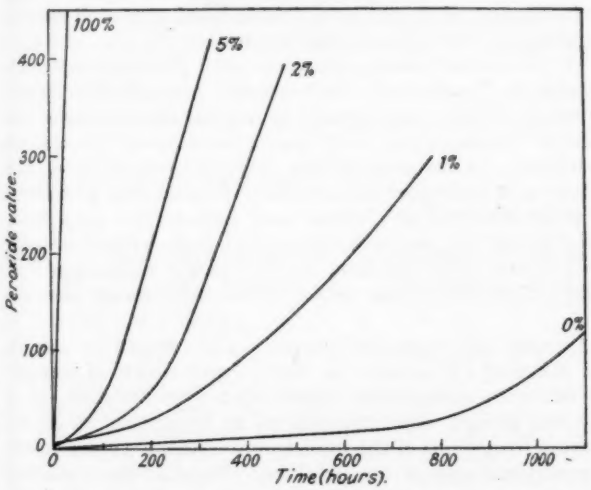
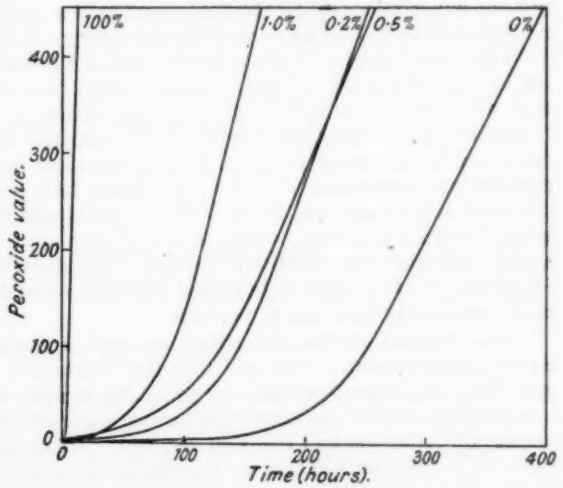


FIG. 2.

Autoxidation of methyl oleate–methyl linoleate mixtures at 50°.



The catalytic nature of the methyl oleate oxidation in the present study, and the probable nature of the oxidising catalyst, are briefly considered. It may first be pointed out that the peroxide values reached in these experiments do not represent maximum values, since oxidation was still proceeding in all cases at an approximately steady linear rate when they were terminated; nevertheless, the values reached are in each instance much in excess of that due exclusively to monohydroperoxide from the linoleate present (*e.g.*, the peroxide value due to complete transformation of 5% of linoleate into monohydroperoxide is 153, and correspondingly less for smaller proportions of the diethenoid ester). Next, it appears that the amount of diethenoid conjugation rises to a point at which it remains approximately constant, and at which it is proportionately higher than the maximum value reached with pure methyl linoleate (*J.*, 1945, 836). The spectrographic measurements on which this statement is based could only be made with sufficient accuracy on the mixture at 20° in which 5% of methyl linoleate was present, but here it appeared that a constant value of $E^{1\%}_{1cm.}$ at 234 mμ of about 20 was attained [corresponding to about 1·7% of diethenoid conjugation in the mixture, or about 34% on the linoleate present as compared with 23% maximum diethenoid conjugation observed (*loc. cit.*) with 100% methyl linoleate] :

Methyl oleate with 5% *methyl linoleate at* 20°.

Peroxide values	101	201	250	334	395	460	525
$E^{1\%}_{1cm.}$ at 234 mμ	9·7	15·0	17·5	22·1	19·8	20·5	19·8

The relatively high proportion of methyl linoleate present as diconjugated compound indicates that in dilute methyl oleate solution the conjugated form less readily undergoes further transformation than when methyl linoleate itself is autoxidised.

We now mention some considerations which have led us recently to modify, or to extend, current opinion on the probable mechanism of the addition of oxygen to the systems $-CH_2{\cdot}CH{:}CH{\cdot}CH_2-$ and $-CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2-$. Farmer and Sutton (*J.*, 1943, 119, 122) showed that the product of addition of oxygen to methyl oleate is the monohydroperoxide of an octadecenoic acid ester in which the peroxido-

group is formed from a methylene group and not at the ethenoid bond, and that hydrogenation of the peroxide yielded a mixture of methyl hydroxystearates. Further, since with polyethenoid esters containing the system $-CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH-$ isomeric rearrangement to conjugated forms was observed, these authors suggested that under the influence of oxygen a hydrogen atom was detached from the reactive methylene group between the double bonds, leaving a system $-CH{:}CH{\cdot}\dot{C}H{\cdot}CH{:}CH-$ which could reappear either in the original or in the conjugated form. In either case Farmer and his co-workers have suggested that autoxidation is dependent upon direct union of oxygen with a $-CH_2-$ group, a hydroperoxide $-CH(OOH)-$ being produced therefrom. Recently, however, Bergström (*Nature*, 1945, **156**, 717; *Arkiv Kemi, Min., Geol.*, 1945, **21**, A, Nos. 14, 15) has observed that hydrogenation of methyl linoleate hydroperoxide furnishes a mixture of 9- and 13-monohydroxystearic acid, no 11-hydroxystearic acid being obtained. Bergström concluded that an initially produced 11-hydroperoxido-octadeca-9 : 12-dienoate must undergo rapid rearrangement into a mixture of 9-hydroperoxido-octadeca-10 : 12-dienoate and 13-hydroperoxido-octadeca-9 : 11-dienoate.

Dr. J. P. W. Houtman, of the Laboratory for Chemical Engineering of the Delft Technical University (Holland), has had some discussion recently with us as to the possible mechanism by which molecular oxygen at room temperature should effect the detachment of a hydrogen atom or a proton from a reactive methylene group, in the course of which he suggested that initial interaction between oxygen and an ethenoid bond might nevertheless prove to be the determining factor. It appears to us that this conception in fact affords a more consistent explanation of autoxidation phenomena in these unsaturated systems than that of direct hydroperoxide formation at a methylene group, and one which is equally in accordance with the facts at present experimentally established, since initial loose attachment of oxygen at a double bond may well render still more detachable one of the hydrogen atoms on an adjacent carbon atom (methylene group).

This could result, in the case of methyl linoleate, in the direct production of 9- and 13-hydroperoxido-derivatives of a diconjugated ethenoid system, as indicated by Bergström's observations; it would also imply that autoxidation in either mono- or poly-ethenoid systems of the types present in natural fats involves the " displacement " of a double bond with consequent ultimate formation of a hydroperoxide at one of the carbon atoms of the ethenoid group originally attacked by oxygen. In the case of oleic (octadec-9-enoic) acid, the possible products would, on this hypothesis, be a mixture of 9-hydroperoxido-octadec-10-enoic and 10-hydroperoxido-octadec-8-enoic acids. The hydroxystearic acids obtained by Farmer and Sutton (*loc. cit.*) from autoxidised methyl oleate would similarly be a mixture of 9- and 10-, and not of 8- and 11-monohydroxystearic acids. Further, the products obtained by oxidative scission of autoxidised methyl oleate (Atherton and Hilditch, *J.*, 1944, 105) or linoleate (Gunstone and Hilditch, *J.*, 1945, 836) would be the same mono- and di-carboxylic acids on either hypothesis.*

The modified mechanism which we have suggested brings into harmony the action of oxygen on simple unsaturated aliphatic systems of diverse kinds and in different circumstances, since direct union of oxygen and the unsaturated system is generally agreed to occur in conjugated unsaturated systems and, to a considerable extent, in those containing separate ethenoid groups when autoxidised at temperatures above about 80° (Atherton and Hilditch, *loc. cit.*). Its application to systems of the linoleic and linolenic type renders more apparent the mechanism by which the central methylene groups are involved. Finally, the corollary that autoxidation of linoleo- or linoleno-glycerides in the manner suggested necessarily involves the production of a conjugated di(or tri)-ethenoid system also adjacent to a hydroperoxide group appears to have an important bearing upon the mechanism of the conversion of linseed and similar " drying " oils (rich in linoleo- and linolenoglycerides) into polymerised products when exposed as films to the action of atmospheric oxygen. Autoxidised fatty oils of the non-conjugated group (typified by linseed oil) are thus transformed under the influence of atmospheric oxygen into conjugated derivatives, which are entirely analogous to those present in oils (such as tung oil) which contain conjugated (elaeostearic) glycerides and which autoxidise and polymerise extremely readily to hard films (as in varnishes).

Experimental.

Methyl Oleate.—The specimen used had been isolated from the mixed acids of *Allanblackia* fat as described in our previous paper (*J.*, 1945, 836), and was the material (286 g.) mentioned therein as having an iodine value of 83·4.

Methyl Linoleate.—The specimens used, prepared as described (*loc. cit.*), had iodine values of 173·4 and 173·8.

Procedure.—The oxidations were carried out in the apparatus described (*loc. cit.*). Typical data for the peroxide and iodine values observed during the course of the oxidations are given in the tables.

* (*Note, added July 2nd*, 1946.) This paper was submitted before the contributions of Farmer and of Bolland and Gee to the Faraday Society's discussion on oxidation in September 1945 were available (*Trans. Faraday Soc.*, 1946, **42**, 228, 236, 244). Here Farmer has now accepted the view that " there is perhaps good justification for postulating universal *initiation* of autoxidative attack in all the various kinds of olefinic systems by *addition* occurring at double bond centres," and has shown how the α-methylenic reactions characteristic of unconjugated olefins may then be formulated on an intermolecular basis. Bolland and Gee, in kinetic studies of olefin oxidation, similarly state that, of the two possible points of oxidative attack—the double bond, and an active methylene group—the argument that the latter must be the site (because of high yields of α-methylene hydroperoxides) is certainly invalid unless the chain length of the oxidation is extremely short.

These statements concede the point we have chiefly been concerned to make in the present paper, namely, to stress in general terms the initial association of oxygen with a double bond (or one of its carbon atoms), and not with an adjacent methylene group. That such initial association is not inconsistent with possible mechanisms of the ensuing chain-reaction is clearly indicated in the papers referred to above.

Time (hours).	Peroxide value.	I.V. (Wijs).	Time (hours).	Peroxide value.	I.V. (Wijs).	Time (hours).	Peroxide value.	I.V. (Wijs).	Time (hours).	Peroxide value.	I.V. (Wijs).
Oxidations of Methyl Oleate at 20°.											
No methyl linoleate present.			1% *Methyl linoleate present.*			2% *Methyl linoleate present.*			5% *Methyl linoleate present.*		
0·0	0	83·5	0·0	4·4	84·9	0·0	4·6	85·4	0·0	2·3	87·3
317·9	8·4	83·2	50·3	10·3	—	37·1	9·4	85·6	36·6	14·3	88·2
466·8	11·1	82·7	152·9	22·7	—	73·2	15·8	85·8	73·9	24·8	87·5
648·8	17·3	83·1	200·6	33·2	84·2	151·2	34·3	85·7	106·8	64·8	87·6
778·2	25·8	82·8	352·4	73·5	83·6	234·5	77·1	85·0	137·9	93·3	87·0
850·3	33·0	82·5	399·4	99·5	83·7	277·4	123	84·8	171·1	163	87·2
906·7	56·6	83·0	504·0	134	83·7	317·4	158	84·1	240·5	254	86·7
975·2	69·8	83·0	598·3	178	83·5	359·7	214	83·6	280·9	323	85·3
1033·6	85·1	82·5	710·2	247	83·1	402·3	286	83·7	328·1	419	83·9
1106·8	122	82·7	784·0	301	82·6	484·6	396	82·3	371·9	525	81·8
Oxidations of Methyl Oleate at 50°.											
No methyl linoleate present.			0·2% *Methyl linoleate present.*			0·5% *Methyl linoleate present.*			1·0% *Methyl linoleate present.*		
0·0	0·0	83·6									
147·9	11·2	83·3	0·0	3·2	83·9	0·0	4·2	84·5	0·0	2·9	85·3
210·3	41·1	83·4	48·0	8·9	83·6	65·8	24·2	84·0	31·0	11·5	—
256·5	105	82·9	89·5	28·5	83·4	105·0	56·5	—	66·1	43·1	—
303·6	219	81·0	127·9	70·8	83·0	132·3	106	84·3	86·2	92·6	84·1
350·2	336	80·3	163·3	143	83·1	164·6	177	82·6	106·0	158	83·1
399·5	465	79·3	201·3	237	81·8	197·8	269	81·7	126·9	253	82·8
444·1	618	78·5	241·5	406	80·4	234·7	384	80·7	146·9	364	81·3
535·0	963	75·1				265·2	504	79·7	169·8	488	80·2
609·1	1053	72·6									

We thank the Colonial Products Research Council for permission to publish these results, and for a grant to one of us (F. D. G.).

THE UNIVERSITY, LIVERPOOL. [*Received, March 27th,* 1946.]

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223. *Constitution of the Mucilage from the Bark of* Ulmus Fulva (*Slippery Elm Mucilage*). *Part II. The Sugars formed in the Hydrolysis of the Methylated Mucilage.*

By R. E. GILL, E. L. HIRST, and J. K. N. JONES.

The protein-free mucilage has been methylated with thallium hydroxide and methyl iodide. The methyl derivative on hydrolysis gave a mixture of sugars among which 2 : 3 : 4 : 6-tetramethyl, 2 : 4 : 6-trimethyl, and 2 : 3 : 6-trimethyl *d*-galactose, 3 : 4-dimethyl and 4-methyl *l*-rhamnose, and 2 : 3 : 4-trimethyl and 2 : 3-dimethyl *d*-galacturonic acid have been identified. A quantitative examination of these sugars has been made and a provisional structural formula for the carbohydrate portion of the mucilage is suggested.

"SLIPPERY ELM BARK is obtained from *Ulmus Fulva* a tree native to North America. The inner bark, which forms the commercial drug, is marketed in the form of broad flat strips. In addition to the usual anatomical elements (sieve tubes, parenchyma, bast fibres, and rays), slippery elm bark contains special mucilage-containing sacs, considerably larger than the surrounding cells, visible in cross sections under the microscope as rounded cavities scattered irregularly through the tissues" (Solereder's "Systematic Anatomy of the Dicotyledons," English Translation, p. 768). On stirring the bark with boiling water, the mucilage, together with resins, oils, and calcium oxalate, was extracted as a viscous brown solution with a characteristic odour. Addition of alcohol to the extract precipitated the crude polysaccharide as a brown fibrous material which contained calcium oxalate and other impurities. It was purified by dissolving in cold dilute hydrochloric acid and pouring into alcohol; the ash-free, acidic mucilage was thus obtained as a white fibrous precipitate, containing carbon, hydrogen, nitrogen, and sulphur. It dissolved in water giving a colourless viscous solution which did not reduce Fehling's solution.

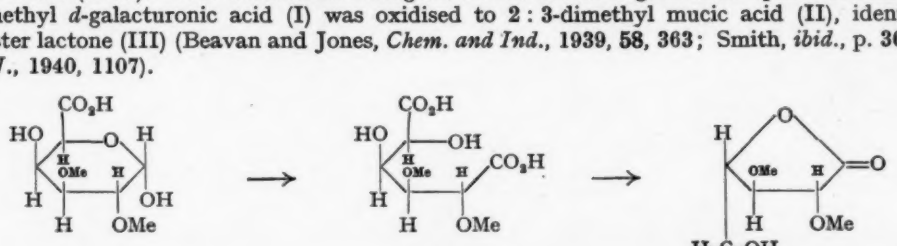
On boiling an aqueous solution of the ash-free polysaccharide it underwent autohydrolysis with considerable reduction in viscosity and precipitation of a brown protein-like solid which contained sulphur and nitrogen. After filtration the solution was poured into alcohol; the sulphur- and nitrogen-free polysaccharide was thus precipitated as a white powder, freely soluble in water and slighly reducing Fehling's solution. This degraded polysaccharide underwent further hydrolysis with N-acid with the formation of reducing sugars (*d*-galactose, *l*-rhamnose, *d*-galacturonic acid) and an aldobionic acid.

In Part I of this series (Gill, Hirst, and Jones, *J.*, 1939, 1469) the isolation of this aldobionic acid from slippery elm mucilage was described. It was shown that complete methylation followed by hydrolysis gave 2 : 3 : 4-trimethyl *d*-galacturonic acid and 3 : 4-dimethyl *l*-rhamnose, and it followed, therefore, that the aldobionic acid present in the mucilage was 2-*d*-galacturonosido-*l*-rhamnose, identical with the aldobionic acid present in flax seed mucilage (Tipson, Christman, and Levene, *J. Biol. Chem.*, 1939, **128**, 609).

It was not found possible to prepare a satisfactory acetyl derivative, and methylation of the mucilage with sodium hydroxide and methyl sulphate resulted in the removal of the protein-like portion of the mucilage

with formation of a partially methylated polysaccharide closely resembling that formed from the methylation of autohydrolysed mucilage. Attempts were made, therefore, to methylate the autohydrolysed polysaccharide. Direct methylation with sodium hydroxide and methyl sulphate was unsatisfactory, as was an attempt to methylate the nitrate ester of the mucilage with the same reagents. Methylation was achieved, however, by the use of thallium hydroxide, thallium ethoxide, and methyl iodide (Menzies, *J.*, 1926, 937; Hirst and Jones, *J.*, 1938, 496). The fully methylated material was isolated finally as a homogeneous, crisp, pale cream powder, soluble in benzene, alcohol, acetone, chloroform, and cold water.

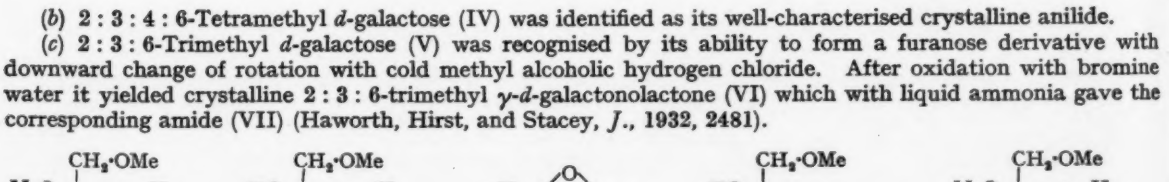
The isolation, estimation, and identification of the sugars present in the methylated polysaccharide was not a simple matter. Complete hydrolysis was difficult and was accompanied by much decomposition, and isolation of pure fractions of methylated sugars was complicated by the formation of constant-boiling mixtures. The free sugars and their glycosides did not crystallise well and it was necessary, therefore, to convert the sugars into well-characterised, crystalline derivatives such as anilides, lactones, and amides. Since, of necessity, the yields of these derivatives were not quantitative, estimates only of the relative amounts of sugars present could be made. Where possible these estimated amounts were checked by polarimetric observations. The calculated amounts of the various sugars identified indicated that they were present in the approximate proportions indicated below and from these figures one of many possible formulæ which will fit the known facts has been suggested (Hirst, *J.*, 1942, 78). (*a*) 2 : 3-Dimethyl *d*-galacturonic acid (4 parts), (*b*) 2 : 3 : 4 : 6-tetramethyl *d*-galactose (2 parts), (*c*) 2 : 3 : 6-trimethyl *d*-galactose (1 part), (*d*) 2 : 4 : 6-trimethyl *d*-galactose (1 part), (*e*) 3 : 4-dimethyl *l*-rhamnose (2 parts), (*f*) 4-methyl *l*-rhamnose (2 parts), and (*g*) 2 : 3 : 4-trimethyl *d*-galacturonic acid (trace). The constitution assigned to the above sugars rests upon the following facts: (*a*) 2 : 3-Dimethyl *d*-galacturonic acid (I) was oxidised to 2 : 3-dimethyl mucic acid (II), identified as its crystalline ester lactone (III) (Beavan and Jones, *Chem. and Ind.*, 1939, **58**, 363; Smith, *ibid.*, p. 363; Luckett and Smith, *J.*, 1940, 1107).



(I.) (II.) (III.)

(*b*) 2 : 3 : 4 : 6-Tetramethyl *d*-galactose (IV) was identified as its well-characterised crystalline anilide.

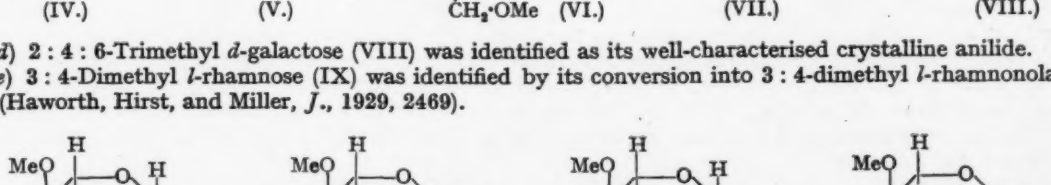
(*c*) 2 : 3 : 6-Trimethyl *d*-galactose (V) was recognised by its ability to form a furanose derivative with downward change of rotation with cold methyl alcoholic hydrogen chloride. After oxidation with bromine water it yielded crystalline 2 : 3 : 6-trimethyl γ-*d*-galactonolactone (VI) which with liquid ammonia gave the corresponding amide (VII) (Haworth, Hirst, and Stacey, *J.*, 1932, 2481).



(IV.) (V.) (VI.) (VII.) (VIII.)

(*d*) 2 : 4 : 6-Trimethyl *d*-galactose (VIII) was identified as its well-characterised crystalline anilide.

(*e*) 3 : 4-Dimethyl *l*-rhamnose (IX) was identified by its conversion into 3 : 4-dimethyl *l*-rhamnonolactone (X) (Haworth, Hirst, and Miller, *J.*, 1929, 2469).

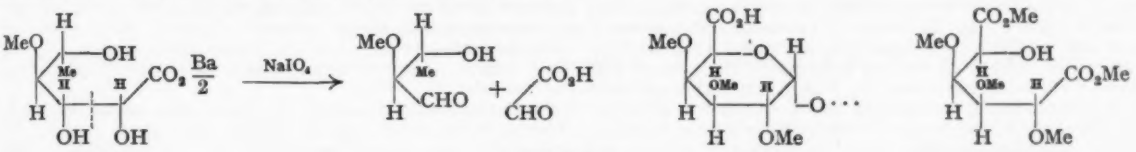


(IX.) (X.) (XI.) (XII.)

(*f*) The monomethyl *l*-rhamnose (XI) was oxidised by bromine water to a crystalline lactone (XII) which from its rotation and rate of mutarotation appeared to be a δ-lactone. The barium salt (XIIa) of the acid was oxidised by sodium periodate with the formation of glyoxylic acid (XIIb). These two observations indicate that there must be a methoxyl group on C_4. Further, the amide obtained by the action of methyl alcoholic ammonia on the lactone (XII) gave a positive Weerman test proving the presence of a hydroxyl group on C_2. Since acetaldehyde was not produced on oxidation of the barium salt (XIIa) with sodium periodate there cannot be a methoxyl group on C_3. It follows that the sugar is 4-methyl *l*-rhamnose (XI)

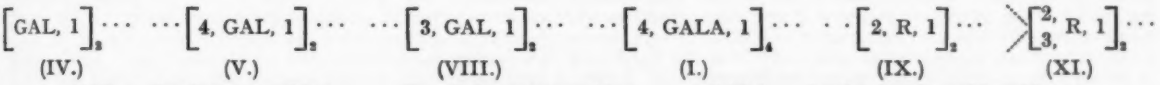
which was first reported by Levene and Compton (*J. Biol. Chem.*, 1936, **114**, 16). The crystalline lactone obtained by oxidation of (XI) was therefore 4-methyl *l*-rhamnonolactone (XII).

(*g*) **2 : 3 : 4-Trimethyl** *d*-galacturonic acid (XIII) was identified after oxidation and esterification as the dimethyl ester of **2 : 3 : 4-trimethyl mucic acid** (XIV).



(XIIa.) (XIIb.) (XIII.) (XIV.)

From the above evidence it is apparent that the repeating unit of slippery elm mucilage must be built up of the following residues linked together in the positions indicated, the precise order of arrangement being as yet undefined :



(IV.) (V.) (VIII.) (I.) (IX.) (XI.)

GAL = *d*-galactose residue. R = *l*-rhamnose residue. GALA = *d*-galacturonic acid residue.

It is of interest to note that in slippery elm mucilage the **1 : 3**-linkage occurs along with **1 : 4-** and **1 : 2-**linkages, and that galacturonic acid and not glucuronic acid is responsible for the acidity of the molecule. In this respect the polysaccharide appears to be a link between the plant gums and the pectin materials. The polysaccharide is similar to other mucilages in that it appears to have properties closely resembling those of the mucoproteins and bacterial polysaccharides (Stacey, *Chem. and Ind.*, 1943, **62**, 110).

Experimental.

Methylation.—The autohydrolysed polysaccharide (nitrogen and sulphur free) (Gill, Hirst, and Jones, *loc. cit.*) had $[\alpha]_D^{20°}$ + 68° in water (*c*, 1·0), equiv. wt. by titration 486, uronic anhydride 36·6%, furfural and methylfurfural 18%, methylfurfural approximately 12%. Preliminary attempts to methylate the autohydrolysed product by means of 30% sodium hydroxide and methyl sulphate were unsuccessful. With fuming nitric acid the mucilage gave an acetone-soluble nitro-derivative. Attempts to methylate this by means of 30% sodium hydroxide and methyl sulphate were also unsuccessful and the following method of methylation was therefore adopted.

The polysaccharide (40 g.) was dissolved in water (200 c.c.) and a hot solution of 4·2N-thallous hydroxide (330 c.c.) was added. The precipitated thallium complex was filtered off, washed with methyl alcohol, and dried in a vacuum at 40° for 18 hours. The solid (252 g.) was powdered (120 mesh) and boiled under reflux with methyl iodide for 15 hours. Excess of methyl iodide was distilled off and 1·4N-thallous hydroxide (300 c.c.) was added to the solid residue and the whole evaporated to dryness at 50°/12 mm. The residue was powdered (120 mesh) and boiled with methyl iodide for 20 hours. At the end of this time the insoluble material reacted neutral to litmus. Excess of methyl iodide was distilled off, and to the residue dissolved in alcohol N-thallium ethoxide in benzene (700 c.c.) was added. The solvents were removed under reduced pressure and the powdered product was boiled with methyl iodide for 15 hours. After distillation of excess of methyl iodide the solid (*X*) was exhaustively extracted with acetone and with chloroform. Evaporation of the solvent gave a partially methylated mucilage (37·4 g.) (Found : OMe, 37·5%). The solid residue (*X*, above) was extracted with water and the extracts concentrated and added to the partially methylated material (37·4 g.) obtained above. The combined products were evaporated to dryness with a benzene solution of N-thallium ethoxide (280 c.c.) and the residue boiled with methyl iodide for 15 hours. The methylated polysaccharide (37·5 g.) was isolated in the usual manner (Found : OMe, 40; ash, 0·01%).

Fractionation.—The methylated polysaccharide (37·4 g.) was dissolved in chloroform (80 c.c.) and fractionally precipitated by gradual addition of light petroleum (b. p. 40—60°) giving *Fraction I* (2·7 g.) : $[\alpha]_D^{20°}$ + 52° in water (*c*, 1·47); OMe, 39·6%. *Fraction II* (9·3 g.) : $[\alpha]_D^{20°}$ + 52° in water (*c*, 1·59); equiv. wt. (by titration with 0·01N-sodium hydroxide), 644; uronic anhydride (from carbon dioxide liberated on boiling with 12% hydrochloric acid), 27·3; OMe, 38·0%. *Fraction III* (17·9 g.) : $[\alpha]_D^{20°}$ + 55° in water (*c*, 1·64); equiv. wt., 595; uronic anhydride, 29·6; OMe, 40·7%. *Fraction IV* (6·2 g.) : $[\alpha]_D^{20°}$ + 55° in water (*c*, 1·5); equiv. wt., 587; uronic anhydride, 30·0; OMe, 39·5%. A completely methylated polysaccharide containing equimolecular amounts of *l*-rhamnose, *d*-galactose, and *d*-galacturonic acid would have equiv. wt., 596; uronic anhydride, 29·5; OMe, 41·6%. From the constants cited for the above four fractions, it was concluded that the methylated material was essentially homogeneous and they were therefore combined.

Hydrolysis of the Methylated Polysaccharide.—Complete hydrolysis of the methylated material was very difficult and after a number of trials the method given below was found to be the most satisfactory. The polysaccharide (32·3 g.) was boiled with 3% methyl alcoholic hydrogen chloride (100 c.c.) for 8 hours. Owing to darkening of the solution, it was not possible to follow the course of the hydrolysis with the polarimeter. The cooled solution was neutralised with silver carbonate, filtered, and evaporated at 40°/12 mm. to a syrup (32·6 g.). Extraction of this with light petroleum gave a soluble syrup (*A*, 25·05 g.) [$n_D^{16°}$ 1·4600; $[\alpha]_D^{20°}$ + 38° in water (*c*, 1·2); equiv. wt., 549; OMe, 48·9%] and an insoluble residue (8·06) which was further hydrolysed by boiling with 3% methyl alcoholic hydrogen chloride. The solution was neutralised with silver carbonate and worked up in the usual manner and the resulting syrup (8·01 g.) extracted with ether giving a red viscous syrup (*B*, 7·25 g.) {$[\alpha]_D^{20°}$ + 39° in methyl alcohol (*c*, 1·5); equiv. wt., 375; OMe, 36·9%} and a solid residue (0·77 g.) which was not further examined.

The syrup (*A*, 25·0 g.) was dissolved in a slight excess of 0·4N-barium hydroxide (150 c.c.) and the solution heated at 100° for 5 hours. The hot solution was neutralised with carbon dioxide, filtered, and the filtrate exhaustively extracted with ether; concentration of the extracts gave a yellow mobile syrup (1·67 g.). The aqueous solution was then evaporated at 40°/12 mm. to a small volume (30 c.c.) and exhaustively extracted with chloroform. The chloroform extracts were combined with the ether extracts (1·67 g.) and the solvent evaporated under reduced pressure, leaving an orange syrup (*C*, 12·54 g., $n_D^{17°}$ 1·4580). Concentration of the aqueous solution gave the barium salts (14·1 g.) as a light brown powder. The barium salts (*D*) were exhaustively extracted with ether to remove the last traces of sugar (*E*, 0·74 g.; $n_D^{18°}$ 1·4718)

(obtained on evaporation of the solvent), and then dried in a vacuum for 8 hours (12·47 g.) (Found: Ba, 21·0; OMe, 31·0. Calc. for the barium salt of 2 : 3-dimethyl methyl-*d*-galacturonoside: Ba, 22·6; OMe, 30·6%).

The syrup (*B*, 7·2 g.) was heated with 0·3N-barium hydroxide (60 c.c.) for 5 hours, and the hot solution neutralised with carbon dioxide and the material separated into sugars (F_1, 1·20 g., $n_D^{18°}$ 1·4630) and barium salts (G_1, 7·08 g.) (Ba, 18·0; OMe, 25%) (for details of separation, see above). It was apparent from these analytical figures that some sugar was attached to the uronic acid in the barium salt (G_1) and this was therefore boiled with 4% methyl alcoholic hydrogen chloride (150 c.c.) for 24 hours. The cooled solution was then neutralised with silver carbonate, filtered, and evaporated to a solid which was exhaustively extracted with acetone. Concentration of the extracts gave a syrup (6·0 g.), which was heated with 0·3N-barium hydroxide (100 c.c.) at 100° for 5 hours. The solution, worked up as described above, gave an ether-soluble syrup (F_2, 1·20 g.) and ether-insoluble barium salts (G_2, 5·0 g.).

Identification of the Barium Salts.—A portion (12·4 g.) of the barium salts (*D*) from fraction *A* was boiled with 4% methyl alcoholic hydrogen chloride (200 c.c.) for 5 hours. The cooled solution was neutralised with silver carbonate, filtered, and the filtrate evaporated at 40°/20 mm. to a syrup which was exhaustively extracted with acetone. The extracts gave on concentration a syrup (9·96 g.), n_D^{19} 1·4627 (Found: equiv. wt., 280. Calc. for the dimethyl ester of 2 : 3-dimethyl methyl-*d*-galacturoside: equiv. wt., 250). The syrup was fractionally distilled in a vacuum giving *Fraction* 1: a mixture of the methyl esters of 2 : 3 : 4-trimethyl methyl-*d*-galacturonoside and 2 : 3-dimethyl methyl-*d*-galacturonoside (0·39 g.); b. p. 156° (bath temp./0·07 mm.); $n_D^{18°}$ 1·4490; $[\alpha]_D^{20°}$ − 13° in water (Found: equiv. wt., 254; OMe, 52·0. Calc. for $C_{11}H_{20}O_7$: equiv. wt., 264; OMe, 58·7%). *Fraction* 2 (3·00 g.): methyl ester of 2 : 3-dimethyl methyl-*d*-galacturonoside; b. p. 158° (bath temp.)/0·05 mm.; $n_D^{18°}$ 1·4532; $[\alpha]_D^{20°}$ − 15° (in water) (equiv. wt., 266; OMe, 52·2%). *Fraction* 3 (2·38 g.): methyl ester of 2 : 3-dimethyl methyl-*d*-galacturonoside; b. p. 165° (bath temp.)/0·05 mm.; $n_D^{18°}$ 1·4553; $[\alpha]_D^{20°}$ − 18° (in water) (equiv. wt., 260; OMe, 52·0%). *Fraction* 4 (0·54 g.): b. p. 170° (bath temp.)/0·005 mm.; $n_D^{18°}$ 1·4572; $[\alpha]_D^{20°}$ ±0° (in water) (equiv. wt., 255; OMe, 50·0%). *Fraction* 5 (1·10 g.): b. p. 190° (bath temp.)/0·03 mm.; $n_D^{18°}$ 1·4701; $[\alpha]_D^{20°}$ + 52° (in water) (equiv. wt., 262; OMe, 50·0%). *Fraction* 6 (1·07 g.): b. p. 230° (bath temp.)/0·04 mm.; $n_D^{18°}$ 1·4761; $[\alpha]_D^{20°}$ + 50° (in water) (equiv. wt., 330; OMe, 47·8%). *Fraction* 7: still residue, 1·07 g.

The constants for fraction 6 indicated that it was mainly disaccharide in nature while those for fractions 1, 2, 3, 4, and 5 were very near to those required for the methyl ester of 2 : 3-dimethyl methylgalacturonoside (Calc.: OMe, 49·6%). The methoxyl values of the first five fractions suggest, however, that they are contaminated with small amounts of the methyl ester of 2 : 3 : 4-trimethyl methylgalacturonoside (Calc.: OMe, 58·7%).

The fractions were hydrolysed individually with N-hydrochloric acid. Fraction 1 changed from $[\alpha]_D^{20°}$ − 13° to + 54° in 2½ hours. Fractions 2, 3, 4, 5, and 6 each became constant at $[\alpha]_D^{20°}$ + 67° after 3 hours.

The solutions obtained from the hydrolysis of the first five fractions were combined, neutralised with silver carbonate, filtered before and after the passage of hydrogen sulphide, and evaporated to a syrup. Fraction 6 was neutralised with barium carbonate, filtered, and evaporated to dryness. The solid residue was exhaustively extracted with ether, some syrupy sugar (0·1 g.) being thereby removed. The extracted barium salt was dissolved in water, barium removed as sulphate by the addition of the calculated quantity of N-sulphuric acid, and the filtered solution added to the syrup obtained from fractions 1, 2, 3, 4, and 5 and the whole evaporated to a syrup (5·65 g.), $[\alpha]_D^{14°}$ + 62° in water (*c*, 1·07) (Found: equiv. wt., 224; OMe, 29. Calc. for 2 : 3-dimethyl *d*-galacturonic acid: equiv. wt., 222; OMe, 27·9%).

The syrup (5·59 g.) was dissolved in water (20 c.c.) and oxidised with bromine (5 c.c.) for 10 hours. Excess of bromine was removed by aeration; the solution was then neutralised with silver carbonate and filtered before and after the passage of hydrogen sulphide. The solvent was then removed at 40°/20 mm. and the residual syrup boiled with 2% methyl alcoholic hydrogen chloride (150 c.c.) for 6 hours. The cooled solution was neutralised with silver carbonate and worked up in the usual manner to give a syrup (4·7 g.), which was distilled in a vacuum giving: *Fraction* 8 (0·37 g.): mainly the dimethyl ester of 2 : 3 : 4-trimethyl *d*-mucic acid; b. p. 140° (bath temp.)/0·001 mm.; $n_D^{19°}$ 1·4545 (Found: OMe, 50%). This fraction crystallised on standing and gave the dimethyl ester of 2 : 3 : 4-trimethyl *d*-mucic acid (0·1 g.), m. p. and mixed m. p. 101° after recrystallisation from ether. *Fraction* 9 (4·1 g.): γ-lactone methyl ester of 2 : 3-dimethyl *d*-mucic acid, b. p. 150° (bath. temp.)/0·001 mm.; $n_D^{19°}$ 1·4640 (Found: OMe, 39·1. Calc. for $C_9H_{14}O_7$: OMe, 39·8%). This fraction crystallised on nucleation with an authentic specimen, giving the γ-lactone methyl ester of 2 : 3-dimethyl mucic acid, m. p. and mixed m. p. 92° after recrystallisation from ether; $[\alpha]_D^{20°}$ − 39°, falling to − 34° (76 hours); − 27° (100 hours); − 22° (124 hours); − 13° (11 days); − 4° (17 days).

From the above methoxyl values, it may be calculated that the acids in fraction (*D*) consisted approximately of 2 : 3 : 4-trimethyl *d*-galacturonic acid (10%) and 2 : 3-dimethyl *d*-galacturonic acid (90%).

The barium salts (G_2) were combined with fraction 7 (1·07 g.) and the whole refluxed with 4% methyl alcoholic hydrogen chloride (150 c.c.) for six hours. The solution was neutralised with silver carbonate and worked up in the manner described above and the syrup (6·1 g.) distilled in a vacuum giving: *Fraction* 10 (2·20 g.): the methyl ester of 2 : 3-dimethyl *d*-galacturonoside, b. p. 135° (bath temp.)/0·001 mm.; $n_D^{19°}$ 1·4579; $[\alpha]_D^{20°}$ + 7° in water (*c*, 1·15) (equiv. wt., 257; OMe, 49·0%). *Fraction* 11 (1·10 g.): b. p. 165° (bath temp.)/0·001 mm.; $n_D^{19°}$ 1·4652; $[\alpha]_D^{20°}$ − 2° in water (*c*, 1·12) (equiv. wt., 261; OMe, 43·6%). The still residue (2·6 g.) appeared to consist mainly of unhydrolysed polysaccharide.

These two fractions were combined and hydrolysed with N-hydrochloric acid (50 c.c.) for 5 hours; $[\alpha]_D^{20°}$ rose from + 2° to + 65° (constant value). The free acids were isolated, oxidised with bromine water, esterified with methyl alcoholic hydrogen chloride (see above for details), and the resulting esters (3·0 g.) distilled in a vacuum, giving the γ-lactone methyl ester of 2 : 3-dimethyl *d*-mucic acid (2·0 g.), b. p. 160° (bath temp.)/0·001 mm.; $n_D^{21°}$ 1·4545 (superfused liquid); OMe, 37·8%; m. p. and mixed m. p. 92° with an authentic specimen, after recrystallisation from ether. The dimethyl ester of 2 : 3 : 4-trimethyl *d*-mucic acid appeared to be absent from this fraction.

It would appear from these experimental results that the acidic fractions obtained after hydrolysis of the methylated polysaccharide consisted mainly of 2 : 3-dimethyl *d*-galacturonic acid along with some 7% of 2 : 3 : 4-trimethyl *d*-galacturonic acid which may have been present as an end-group in the original methylated polysaccharide.

Identification of the Sugars.—The methyl glycosides (*C*, 12·47 g.), $n_D^{17°}$ 1·4580, were fractionally distilled in a vacuum giving *Fraction* 12 (9·27 g.): tetramethyl and trimethyl methyl-*d*-galactosides, b. p. 120—130° (bath temp.)/0·001 mm.; $n_D^{18°}$ 1·4530; $[\alpha]_D^{20°}$ + 80° in water; OMe, 56·8%. *Fraction* 13 (2·68 g.): trimethyl methyl-*d*-galactoside, dimethyl-*l*-rhamnoside, and monomethyl methyl-*l*-rhamnoside, b. p. 130—150° (bath temp.)/0·001 mm.; $n_D^{18°}$ 1·4620; $[\alpha]_D^{20°}$ + 29° in water; OMe, 44·3%. Still residue, 0·40 g.

Fraction 12 was dissolved in N-hydrochloric acid (100 c.c.) and heated at 90—95° for 3 hours. $[\alpha]_D^{18°}$ rose from + 80° to + 110° (20 mins.) and then fell to + 90° (constant value). The solutions were neutralised with silver carbonate, filtered before and after the passage of hydrogen sulphide, and evaporated at 40°/12 mm. to a syrup (*H*) (8·2 g.), $n_D^{18°}$ 1·4700; $[\alpha]_D^{19°}$ + 44° rising to + 66° in 1% methyl alcoholic hydrogen chloride (after 26 hours); OMe, 46·0%.

The syrup (*H*) (0·96 g.) on heating with aniline (0·41 g.) in alcohol (30 c.c.) for 2 hours gave on cooling a mixture of anilides. By fractional crystallisation from alcohol 2 : 3 : 4 : 6-tetramethyl *d*-galactose anilide (0·65 g.) was isolated, m. p. and mixed m. p. 194° (Found: OMe, 40·6. Calc. for $C_{16}H_{25}O_5N$: OMe, 39·9%), and 2 : 4 : 6-trimethyl *d*-galactose

anilide (0·10 g.), m. p. and mixed m. p. 179° (Found: OMe, 29·2. Calc. for $C_{15}H_{23}O_5N$: OMe, 31·3%). (Proof of identity was confirmed by an *X*-ray analysis of the crystals for which we are indebted to Dr. T. Malkin.)

Another sample of the syrup (*H*) (1·5 g.) was dissolved in water (10 c.c.) and oxidised with bromine (2 c.c.) at 50° for 6 hours. The mixed galactonic acids were isolated as a syrup (1·45 g.) in the usual manner and distilled in a vacuum giving 2 : 3 : 4 : 6-tetramethyl, 2 : 4 : 6-trimethyl, and 2 : 3 : 6-trimethyl *d*-galactonolactones as a syrup (1·0 g.), b. p. 125—150° (bath temp.)/0·001 mm.; $[\alpha]_D^{20°}$ + 85° in water (*c*, 1·0, initial value); + 6° (24 hours, constant value) (Equiv. wt., 225; OMe, 48·0%). The syrup crystallised on standing and was drained on a porous tile giving 2 : 3 : 6-trimethyl *d*-galactonolactone (0·40 g.), m. p. 98° (after sublimation in a vacuum), not depressed on admixture with an authentic specimen; $[\alpha]_D^{20°}$ − 40° (initial value, *c*, 2·1 in water); − 35° (30 hours); − 30° (3 weeks) (Found: OMe, 43·0. Calc. for $C_9H_{16}O_6$: OMe, 42·3%).

2 : 3 : 4-Trimethyl *d*-galactose was absent from the mixture since the syrup (*H*) (1·54 g.) after conversion into the mixed glycosides with methyl alcoholic hydrogen chloride did not give a positive reaction for the presence of a $-CH_2{\cdot}OH$ group on heating its *p*-toluenesulphonyl derivative with sodium iodide in acetone (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366).

These results, taken in conjunction with refractive indices, methoxyl values, and rotations of the mixed sugars, mixed glycosides, and mixed lactones, indicate the presence of some 50% of 2 : 3 : 4 : 6-tetramethyl *d*-galactose in fraction 12, together with some 50% of trimethyl *d*-galactose of which approximately half is 2 : 3 : 6-trimethyl *d*-galactose and the remainder 2 : 4 : 6-trimethyl *d*-galactose.

Fraction 13 was hydrolysed with N-hydrochloric acid and the sugars (2·1 g.) were isolated in the usual manner; $[\alpha]_D^{19°}$ + 31° in water (*c*, 1·0); OMe, 33·5%. This syrup gave no crystalline anilide on heating with an alcoholic solution of aniline, showing the absence of any large percentage of 2 : 4 : 6-trimethyl, 2 : 3 : 4-trimethyl, or 2 : 3 : 4 : 6-tetramethyl *d*-galactose. The syrup (1·7 g.) was therefore oxidised with bromine water and the resulting acids, isolated in the usual manner, were lactonised by heating at 100°/5 mm. for 3 hours; the lactones then crystallised. The crystals (1·2 g.) which were mainly, if not entirely, a mixture of 3 : 4-dimethyl *l*-rhamnonolactone and 2 : 3 : 6-trimethyl *d*-galactonolactone, had m. p. 70—90°; $[\alpha]_D^{20°}$ − 57° in water (*c*, 3·1, initial value) falling to − 27° (8 days). By solution of the mixed lactones in liquid ammonia, a mixture of the corresponding crystalline amides was obtained. This was separated into its components by fractional crystallisation from methyl alcohol–acetone–ether giving 3 : 4-dimethyl *l*-rhamnonamide, m. p. and mixed m. p. 153°, and 2 : 3 : 6-trimethyl *d*-galactonamide, m. p. and mixed m. p. 135° (Haworth, Raistrick, and Stacey, *Biochem. J.*, 1937, **31**, 644), respectively. With sodium hypochlorite the amides gave cyanic acid, proving the presence of an amide with a free α-hydroxyl group (Weerman, *Rec. Trav. chim.*, 1917, **37**, 16).

The mixed lactones (0·30 g.) on oxidation with periodic acid (a reagent diagnostic for αβ-glycols) gave no formaldehyde or acetaldehyde (dimedon), thereby proving the absence of 2 : 3-dimethyl *l*-rhamnonolactone and 2 : 3 : 4-trimethyl *d*-galactonolactone.

The mixture of lactones was separated into its components by a tedious process of repeated crystallisation and fractional sublimation giving small quantities of 3 : 4-dimethyl *l*-rhamnonolactone, m. p. 74°, mixed m. p. with an authentic specimen, 76°, $[\alpha]_D^{20°}$ − 158° (initial value in water), and 2 : 3 : 6-trimethyl *d*-galactonolactone, m. p. and mixed m. p. 98°, $[\alpha]_D^{20°}$ − 40° in water.

From an examination of the methoxyl values and refractive indices it may be calculated that fraction 13 contains some 75% of 3 : 4-dimethyl *l*-rhamnose and 25% of 2 : 3 : 6-trimethyl *d*-galactose

Fractions *E* (0·74 g.), F_1 (1·20 g.), F_2 (1·20 g.), the syrup from fraction 6 (0·10 g.), and the residue (0·40 g.) from the distillation of fraction *C* were combined, boiled under reflux with 2% methyl alcoholic hydrogen chloride, neutralised with silver carbonate, and the product (3·40 g.), isolated in the usual manner, was distilled in a vacuum giving 3·0 g., b. p. 140—150° (bath temp.)/0·001 mm.; $n_D^{19°}$ 1·4670; $[\alpha]_D^{20°}$ − 27° (*c*, 1·0 in water) [Found: OMe, 33·0. Calc. for $C_8H_{16}O_5$ (methyl methylrhamnoside): OMe, 32·3%].

The distillate was dissolved in N-hydrochloric acid (50 c.c.) and heated at 90—95° for 4 hours. $[\alpha]_D^{20°}$ rose from − 27° (initial value) to + 28° (constant value). The cooled solution was neutralised with silver carbonate, filtered before and after the passage of hydrogen sulphide, and concentrated to a syrup (2·80 g.), $[\alpha]_D^{20°}$ + 22° in water (*c*, 1·10), which consisted mainly of 4-methyl rhamnose (Found: OMe, 20·3. Calc. for $C_7H_{14}O_5$: OMe, 17·4%).

This material (2·80 g.) was oxidised with bromine (2 c.c.) in water (10 c.c.) for 8 hours at 20°. Excess of bromine was removed by aeration. The product, isolated in the usual manner, crystallised on standing. Recrystallisation from acetone–light petroleum gave the *4-methyl δ-l-rhamnonolactone* in the form of long needles, m. p. 82°; $[\alpha]_D^{20°}$ − 141° in water (*c*, 1·06) falling to − 115° (14 hours, constant value) (Found: C, 47·2; H, 7·1; OMe, 17·2; equiv. wt., 182. $C_7H_{12}O_5$ requires C, 47·7; H, 7·0; OMe, 17·7%; equiv. wt., 176). On reaction with methyl alcoholic ammonia the lactone gave 4-methyl *l*-rhamnonamide as a syrup which gave a positive Weerman raction.

Oxidation of the Barium Salt of 4-Methyl l-Rhamnonic Acid with Sodium Periodate.—The crystalline lactone (13·4 mg.) was titrated with 0·01N-barium hydroxide (7·5 c.c.) and sodium periodate (0·236M, 1 c.c. excess) added. Carbon dioxide was bubbled through the solution and then through 2 : 4-dinitrophenylhydrazine solution. No acetaldehyde derivative formed during two hours. Rhamnose hydrate (19·6 mg.) gave, under the same conditions, a copious precipitate of acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 161°. The solution of the salt of 4-methyl *l*-rhamnonic acid, after oxidation, was freed from periodate and iodate by the addition of barium chloride, filtered, and the filtrate tested for the presence of glyoxylic acid with naphtharesorcinol (Fearon test); a strong positive reaction was obtained.

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THE UNIVERSITY, BRISTOL.
THE UNIVERSITY, MANCHESTER.

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224. *A Method for the Synthesis of Tertiary Aromatic Arsines.*

By W. E. HANBY and WILLIAM A. WATERS.

Aryl diazonium chlorides, or their zinc double salts, $(ArN_2)_2ZnCl_4$, when decomposed, in acetone suspension, by zinc dust in the presence of arsenious chloride, or of a chloroarsine, give good yields of tertiary arsines, *e.g.*:

$$3PhN_2Cl + AsCl_3 + 3Zn = Ph_3As + 3N_2 + 3ZnCl_2$$

The optimum conditions for the synthesis of triphenylarsine from aniline are described, and two examples are given of extensions of the reaction to the synthesis of tertiary arsines which cannot be made so easily by other, previously described, methods.

In 1938 it was shown by one of us (Waters, *Nature*, 1938, **142**, 1077; *J.*, 1939, 867) that aromatic arsenic compounds could be obtained by the direct action of aryl diazonium chlorides on arsenic powder in the presence of acetone. The reaction, however, is not as vigorous as that between aryl diazonium chlorides and antimony (Makin and Waters, *J.*, 1938, 843), and the yield of organo-metallic product is very poor. To obviate this, it was decided to adopt the procedure of Nesmejanov (*Ber.*, 1929, **62**, 1010, 1018; 1935, **68**, 1877) for the preparation of organometallic compounds, and prepare the elementary arsenic *in situ* by the action of zinc dust on arsenious chloride. This method proved to be highly successful: aniline can be converted into triphenylarsine in 65% yield by a single stage process by adding zinc dust to a stirred suspension of zinc benzenediazonium chloride, $(PhN_2)_2ZnCl_4$, in anhydrous acetone containing arsenious chloride. Optimum yields are obtained when the diazonium salt and arsenious chloride are used in equivalent amounts, according to the equation (p. 1029).

If a larger proportion of arsenious chloride is used, the reaction product is a mixture of triphenylarsine with diphenylchloroarsine and phenyldichloroarsine, but though the reaction evidently occurs in stages it does not seem to be practicable to control it to obtain high yields of either of the last two products. Both phenyldichloroarsine and diphenylchloroarsine react, in acetone, with benzenediazonium chloride and zinc dust to give triphenylarsine. Mixed tertiary arsines can be prepared in this way, as illustrated in the experimental section of this paper by the preparation of *diphenyl-β-chlorovinylarsine* from β-chlorovinyldichloroarsine (lewisite-I).

The diazo synthesis of tertiary arsines has not the same limitations as the alternative methods of synthesis involving the use of metallic sodium, or of Grignard reagents, *e.g.*:

$$3PhCl + AsCl_3 + 6Na = Ph_3As + 6NaCl$$

$$Ph_2AsCl + MgEtBr = Ph_2AsEt + MgClBr$$

and, in view of the accessibility of aromatic amines, may prove to be of considerable practical value in synthetic work. The preparation of *tri*-p-*chlorophenylarsine* from *p*-chloroaniline illustrates one such application of the reaction.

Modification of the process by using other metals, or solvents, may of course be possible, but in view of their cheapness and availability it is improbable that zinc dust and acetone can be replaced by more convenient substances. Though the reaction can be effected by using iron filings in place of zinc dust, the yield of triphenylarsine is much less. Again, the reaction will proceed, though not so well, in ethyl acetate. It does not occur in alcohol.

Experimental.

Preparation of Triphenylarsine.—Aniline (300 g., technical quality) in hydrochloric acid (1 l. of concentrated acid + 400 c.c. of water) is diazotised (with 220 g. of sodium nitrite in 250 c.c. of water) and the zinc chloride double salt is precipitated (yield 90%) by adding slowly to the stirred solution at 0° a concentrated solution of zinc chloride (280 g., technical) in dilute hydrochloric acid (120 c.c.). This is filtered off at the pump, pressed free from water, and washed with dry acetone (500 c.c.) until powdery. The retention of even a little moisture at this stage leads to the production of considerable quantities of phenol and tarry by-products, and greatly lowers the final yield.

The dry zinc diazonium chloride (600 g.) is transferred to a large flask, surrounded with a freezing mixture, and stirred vigorously with *dry* acetone (1·5 l.; technical product treated with calcium chloride and decanted is satisfactory) and arsenious chloride (180 g.). Zinc dust (220 g. of 90%) is added in small portions during 2 hours, the temperature being kept below 5°. After being left overnight (or refluxed for 15 minutes) the mixture is filtered, and the filtrate evaporated on a water-bath. The last of the acetone is removed by steam, and the remaining oil is poured into a beaker and stirred with dilute hydrochloric acid (200 c.c.) so that the crude product (300 g.) solidifies in small lumps. This is triphenylarsine of about 68% purity. Pure triphenylarsine can be obtained from this crude solid by melting it under an equal weight of methanol; on cooling the pure product crystallises, leaving all tarry by-products in solution.

Optimum Conditions of Reaction.—The effect of varying the relative quantities of the reagents is shown below:

Yields of arsenicals from 75 g. of aniline.

Quantities of reagents.			Yields of products.		
$AsCl_3$ (g.).	Zn dust (g.).	Acetone (c.c.).	Ph_3As (g.).	% on $PhNH_2$.	% on $AsCl_3$.
27	40	500	34	41	74
36	30	500	39	47	64
45	50	300	52	63	69
45	60	350	56	68	74
49	50	300	52	63	63
72	60	500	Ph_3As, 23·5 g.	Ph_2AsCl, 21 g.	$PhAsCl_2$, 11 g.
100	60	500	,, 8 g	,, 26 g.	,, 20 g.

Tri-p-*chlorophenylarsine.*—This was obtained, by following the same procedure, from *p*-chloroaniline (20 g.), arsenious chloride (9 g.), and zinc dust (10 g.). The *compound* crystallised from light petroleum in needles, m. p. 75°. Yield, 4 g. (Found: C, 52·9; H, 2·95. $C_{18}H_{12}Cl_3As$ requires C, 52·8; H, 2·93%). Its *mercurichloride* crystallised from slightly diluted acetone in white needles, m.p. 235° [Found: C, 31·5; H, 1·72. $(C_6H_4Cl)_3As,HgCl_2$ requires C, 31·7; H, 1·76%].

Diphenyl-β-chlorovinylarsine was prepared in a similar manner from lewisite-I (1 mol.), zinc benzenediazonium chloride (2 mols.), and zinc dust in acetone at 0°. After the removal of the solvent, the product was washed with cold dilute sodium hydroxide solution to decompose any unchanged lewisite, and then was dried and distilled in a vacuum. Fractionation yielded an oil, b. p. 169—170°/3 mm., 161°/2 mm., which was not vesicant (Found: Cl, 12·4; equiv. wt. by iodine titration, 146. $C_{14}H_{12}ClAs$ requires Cl, 12·2%; equiv. wt., 145·3). On being boiled with sodium hydroxide solution it decomposed, evolving acetylene and leaving diphenylarsenoxide.

Note on the Analysis of Aromatic Arsenic Compounds.—The analysis of tervalent aromatic arsenic compounds by titration with iodine in the presence of sodium bicarbonate tends to give trouble, as the oxidation is often slow, but direct titration, in hydrochloric acid, with standard potassium iodate is both rapid and accurate. Individual tertiary arsines are best estimated gravimetrically as their insoluble mercurichlorides, $R_3As,HgCl_2$.

The authors thank the Chief Scientific Officer of the Ministry of Supply for permission to publish this work, which was carried out in 1939—1940.

CHEMICAL DEFENCE RESEARCH DEPARTMENT, MINISTRY OF SUPPLY. [*Received, February 14th*, 1946.]

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225. *Researches in the Phenanthridine Series. Part VII. Quaternary Salts with Urethane and Urea Substituents.**

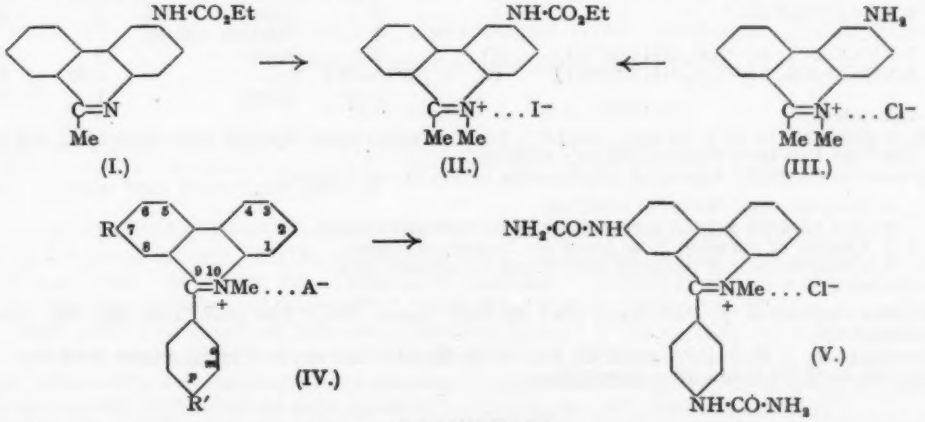
By LESLIE P. WALLS.

(With a Note by C. H. BROWNING, K. M. CALVER, and M. W. LECKIE.)

Previous work has shown that 9-phenylphenanthridinium salts with two amino-groups are powerful trypanocides. Methods have been devised whereby these compounds can be converted into urethanes and ureas. The products are stable crystalline salts, which do not possess much trypanocidal activity in *T. congolense* infections. In some of them, however, a new feature appears: an alleviation of the symptoms in mice due to the important South American parasite, *T. cruzi*, which is resistant to the common trypanocides.

A COMPREHENSIVE study of the phenanthridine series has revealed so far (*J.*, 1945, 294) that quaternary salts of 9-phenylphenanthridine with two amino-groups possess marked curative action in *T. congolense* infections. This trypanosome is resistant to arsenicals and other well-known trypanocides, and the results obtained seemed sufficiently significant to justify an examination of quaternary salts in which the substituent amino-groups are modified. In general, acetylation of these groups has a striking dystherapeutic effect. However, it was decided to examine the corresponding carbalkoxyamino- and carbamido-derivatives because these groups differ in many respects from acylamido-groups. When present in a benzene ring they direct substituents to the *ortho* and *para* positions even in the presence of concentrated sulphuric acid (compare Dikshoorn, *Rec. Trav. chim.*, 1929, **48**, 527); carbalkoxyamino- are far more resistant to hydrolysis than are acylamido-groups. The protection thus afforded the susceptible amino-groups might be reflected in a greater persistence of such compounds in the body of the host, the active diamino-salts being slowly liberated. It is appreciated that so little is known about the mode of action of trypanocides that arguments of this kind have doubtful validity. A further valuable property of these compounds as drugs would be the marked reduction in colour compared with the diamino-salts.

The preparation of the carbalkoxyamino-derivatives may be by two routes. Thus 3-amino-9-methylphenanthridine (Morgan and Walls, *J.*, 1932, 2228) may be converted into the carbethoxyamino-compound (I), and the product methylated by known methods to yield **3-*carbethoxyamino*-9 : 10-*dimethylphenanthridinium iodide*** (II), or the amino-quaternary salt (III) in aqueous soluton may be stirred with ethyl chloroformate for



a few minutes and then treated with potassium iodide. By the latter method the diamino-quaternary salts (compare IV; $R = R' = NH_2$, $A = Cl$) referred to in previous papers of this series have been converted into the corresponding dicarbethoxyamino-salts. These yellow salts are stable, and crystallise well from water, although several of them are markedly thixotropic.

In aqueous solution reaction between the diamino-quaternary salts (compare IV) and cyanic acid is slow, and owing to simultaneous decomposition of the acid yields of the dicarbamido-compounds (compare V) are

* The experimental work described in this paper formed the subject of British provisional patent applications Nos. 14478/43 and 17811/44.

small. The low reactivity of the amino-groups in these salts is shown also by their inertness to nitrourea (Davis and Blanchard, *J. Amer. Chem. Soc.*, 1929, **51**, 1794). Cyanic acid is more stable in 50% acetic acid than in aqueous solution, for reaction went to completion when a solution of (IV; R = R′ = NH_2) in this medium was treated with potassium cyanate. The reverse method, formation of the carbamido-compounds followed by methylation, is unsatisfactory owing to the extremely sparing solubility of the carbamides. This substitution of the amino-groups by carbamido-groups likewise leads to stable crystalline salts, of diminished colour, which have not the bitter taste of the diamino-salts.

*Note on Chemotherapeutic Trypanocidal Action.**—The biological properties of the compounds referred to here were investigated on the same lines as in a previous report (Walls, *J.*, 1945, 294). Nos. **1543**, **1544**, **1569**, **1575**, **1566**, and **1567** are the carbethoxyamino-compounds corresponding to the acetyl derivatives of the same bases (Nos. **896**, **893**, **1507**, **1574**, **1554**, and **1162**) already described. There is generally no striking difference in the toxicity of corresponding compounds in the two series. Both usually have a much lower chemotherapeutic action on *T. congolense* and *T. brucei* than the unsubstituted amino-compounds. The difference is strikingly shown with nos. **1543** and **897**, **1566** and **1565**, **1569** and **1508**, **1575** and **1573**; in each pair less than one-hundredth of the maximum tolerated dose of the unsubstituted amino-compound cures infections with *T. congolense* in a proportion of animals, whereas the corresponding carbethoxyamino-derivatives have at most a slight therapeutic effect in a dose which is one-sixth of the maximum tolerated. The carbomethoxyamino- and also the carbamido-derivatives do not differ greatly from the corresponding carbethoxyamino-analogues (cf. **1544** with **1585** and **1584**; **1543** with **1583**). It is noteworthy, however, that the carbethoxyamino-compound No. **1544** and the corresponding methanesulphonate, in a dose of 3·0—1·2 mg., has a definite therapeutic action on *T. cruzi* in mice (Browning, Calver, Leckie, and Walls, *Nature*, 1946, **157**, 263). Infections with this trypanosome are refractory to other classes of trypanocidal drugs and apart from certain other phenanthridine compounds respond only to Bayer 7602 Ac.

	Formula (IV).		Therapeutic effect in mice infected with *T. congolense* (Strain 1).[1]		*T. brucei*.[2]	
Compound.	Substituents.	Acid radical.	Dose, mg.(a)	Result.	Dose, mg.(a)	Result.
1543	7-NH·CO_2Et-9-*p*-C_6H_4·NH·CO_2Et	Cl	1·43	Cure	1·43	O
			0·22—0·066	Slight—O		
1544	3-NH·CO_2Et-9-*p*-C_6H_4·NH·CO_2Et	Cl	2·85*—1·43	Cure	1·85 *	Cure
			0·5	Slight	1·25	Cure—Slight
					0·5	O
1569	7-NH·CO_2Et-9-*m*-C_6H_4·NH·CO_2Et	Cl	2·5	Cure	2·5	Slight
			1	Marked—Slight		
1575	3-NH·CO_2Et-9-*m*-C_6H_4·NH·CO_2Et	Cl	1	Slight	1	O
1566	2 : 7-NH·CO_2Et-9-Ph	Cl	1	Cure	0·5	O
			0·2	Slight		
1567	3 : 7-NH·CO_2Et-9-Ph	Cl	10 *	Cure	10 *	Slight
			2 *	Slight		
1585	3-NH·CO_2Me-9-*p*-C_6H_4·NH·CO_2Me	Cl	5—1	Cure	5	Cure
			0·33	Slight	1·66	Slight
1599	3-NH·CO_2Et-9-Me	I	2	(Cure)	2	O
			1	Marked—Slight		
1583	7-NH·CO·NH_2-9-*p*-C_6H_4·NH·CO·NH_2	Cl	2	Slight	2	O
1584	3-NH·CO·NH_2-9-*p*-C_6H_4·NH·CO·NH_2	Cl	3·3*—2·5	Cure	1·66	Slight
			1·66	Slight	1	O

* Partly undissolved.

(*a*) Dosage is reckoned per 20 g. of body weight, 1 c.c. of solution being injected subcutaneously; the highest dose shown is not less than half the average maximum tolerated.

The terms used to designate degrees of trypanocidal action are as follows:

Cure = Complete sterilisation of infection.
(Cure) = Cure effected only in a proportion of the animals treated.
Marked = Absence of parasites from blood for 10 days or longer.
Slight = Disappearance of parasites from blood for several days.
O = No effect.

[1] See Browning and Calver, *J. Path. Bact.*, 1943, **55**, 393; Calver, *Trop. Dis. Bull.*, 1945, **42**, 704; treatment was given at the acme stage.

[2] See Browning *et al.*, *J. Path. Bact.*, 1934, **39**, 75; 1938, **46**, 203; the strain of trypanosome used was "Paris III," and treatment was given 24 hours after inoculation.

Experimental.

7-Carbethoxyamino-9-p-carbethoxyaminophenyl-10-methylphenanthridinium Chloride (**1543**).—The diamino-quaternary salts are insoluble in ethyl chloroformate and reaction does not occur in absence of solvent. A solution of 7-amino-9-*p*-aminophenyl-10-methylphenanthridinium chloride (2 g.; *J.*, 1938, 396) in hot water (40 ml.) was cooled rapidly, and before crystallisation occurred a small excess of ethyl chloroformate (1·4 ml.) was stirred in vigorously. The colour of the solution rapidly faded from deep red to yellow and in a few minutes yellow crystals of the *product* separated (2·2 g.). This salt was rather sparingly soluble in water from which it crystallised in transparent deep yellow prisms, m. p. 242° (decomp.) (Found for dried salt: N, 9·0; Cl, 7·35. $C_{36}H_{36}O_4N_3Cl$ requires N, 8·75; Cl, 7·4%).

* Work done with the support of the Medical Research Council in the Department of Bacteriology, The University and Western Infirmary, Glasgow.

The following compounds were similarly prepared from the corresponding diamino-quaternary salts. The m. ps. are dependent on the rate of heating, being with decomposition and effervescence. Most of the salts contain solvent of crystallisation, but analyses refer to dried salts. 3-*Carbethoxyamino*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* (1544) crystallised from water in sparingly soluble buff-coloured needles, m. p. 261° (Found: N, 8·85; Cl, 7·25%). Double decomposition with silver methanesulphonate afforded the corresponding *methanesulphonate* in pale yellow prisms readily soluble in water (Found: N, 7·5. $C_{27}H_{29}O_7N_3S$ requires N, 7·8%). 7-*Carbethoxyamino*-9-m-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* (1569) crystallised from alcohol in yellow needles, m. p. 219° (Found: N, 8·85; Cl, 7·2%). 3-*Carbethoxyamino*-9-m-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* (1575) crystallised from water in pale yellow needles, m. p. 245° (Found: N, 9·15; Cl, 7·55%). 2 : 7-*Dicarbethoxyamino*-9-*phenyl*-10-*methylphenanthridinium chloride* (1566) crystallised from alcohol in orange-yellow needles, markedly thixotropic, m. p. 242°. The solution showed brilliant green fluorescence (Found: N, 8·75; Cl, 7·45%).

3 : 7-*Dicarbethoxyamino*-9-*phenyl*-10-*methylphenanthridinium Chloride* (1567).—This *salt* was purified by dissolving it in hot glacial acetic acid and then diluting with several volumes of hot water. On being cooled the solution deposited minute yellow needles, m. p. 267° (Found: N, 8·85; Cl, 7·45%). 3-*Carbomethoxyamino*-9-p-*carbomethoxyaminophenyl*-10-*methylphenanthridinium chloride* (1585) was prepared similarly with methyl chloroformate. Yellow needles, m. p. 318—323° (decomp.), from water (Found: Cl, 7·9. $C_{24}H_{23}O_4N_3Cl$ requires Cl, 7·85%).

3-*Carbethoxyamino*-9-*methylphenanthridine* (I).—3-Amino-9-methylphenanthridine was readily carbethoxylated by the method of Lesslie and Turner (*J.*, 1933, 1588). The amine (3 g.) and diethylaniline (2·2 g.) were dissolved in absolute alcohol (20 ml.) and treated with ethyl chloroformate (1·9 g.) whereupon there was an immediate precipitation of minute yellow needles. After being refluxed for 20 minutes the solution was poured into water, neutralised by ammonia, and steam-distilled to remove diethylaniline. The product remained in the still as a white crystalline powder (3·1 g.) which was recrystallised from methyl alcohol, forming slightly discoloured prisms, m. p. 179—180° (Found: C, 73·15; H, 5·65; N, 9·75. $C_{17}H_{16}O_2N_2$ requires C, 72·9; H, 5·7; N, 10·0%).

3-*Carbethoxyamino*-9 : 10-*dimethylphenanthridinium Iodide* (II, 1599).—When the foregoing compound (2 g.) was dissolved in nitrobenzene and treated at 150° with methyl sulphate (1 ml.), the quaternary methosulphate crystallised in high yield. Since this salt and the corresponding chloride are extremely soluble in water, the product was characterised as the *iodide*, which crystallised from that solvent in yellow plates, m. p. 209° (decomp.) (Found: N, 6·35; I, 28·15; loss at 100°, 6·0. $C_{18}H_{19}O_2N_2I$, 1·5 H_2O requires N, 6·25; I, 28·25; H_2O, 6·0%).

7-*Carbamido*-9-p-*carbamidophenyl*-10-*methylphenanthridinium Chloride* (V, 1593).—The corresponding diamino-quaternary salt was dissolved in dilute hydrochloric acid, but with either 2 or 4 equivalents of acid at 0·2N or N the yield of reaction with potassium cyanate was very small, decomposition of cyanic acid being the predominant reaction. The following method proved successful: the diamino-salt (2 g.) was dissolved in acetic acid (10 ml. each of glacial acid and water), cooled in ice-water, and treated with potassium cyanate (0·5 g.) dissolved in a small quantity of water. The quality of the cyanate was previously proved by its almost quantitative conversion of aniline into phenylurea. Small crystals began to separate after a few minutes, and after 12 hours the *product* (1·4 g.) was collected, a further yield (0·6 g.) of less pure substance being obtained by dilution of the mother liquor with dilute hydrochloric acid. The salt crystallised from water in deep yellow thin plates, m. p. 265° (decomp.) (Found for dried salt: N, 16·65; Cl, 8·55. $C_{22}H_{20}O_2N_5Cl$ requires N, 16·6; Cl, 8·4%). 3-*Carbamido*-9-p-*carbamidophenyl*-10-*methylphenanthridinium chloride* (1584) was similarly prepared in high yield; it crystallised from water in matted yellow needles, m. p. 276° (decomp.) (Found for dried salt: N, 16·3; Cl, 8·55%).

The work described above has been carried out as part of the research programme of the Chemical Research Laboratory, and this paper is published by permission of the Director of the Laboratory.

CHEMICAL RESEARCH LABORATORY, DEPARTMENT OF SCIENTIFIC AND INDUSTRIAL RESEARCH,
TEDDINGTON, MIDDLESEX. [*Received, April 5th*, 1946.]

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226. *The Preparation of Quinoline Derivatives from Aromatic Amines and Ethyl Ethoxymethylenemalonate.*

By K. SCHOFIELD and J. C. E. SIMPSON.

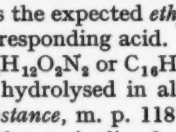
Interaction of aniline (or *p*-anisidine) and ethyl ethoxymethylenemalonate, followed by cyclisation, gives *ethyl 4-hydroxyquinoline-3-carboxylate* (II; R = H; R′ = Et) [or its 6-*methoxy*-derivative (II; R = OMe; R′ = Et)], together with unidentified *products*.

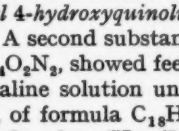
WORK on 4-hydroxycinnoline-3-carboxylic acid (I; R = H) and its 6-methoxy-derivative (I; R = OMe) (Schofield and Simpson, this vol. p. 472), necessitated the preparation of the corresponding quinoline acids (II; R = H and OMe; R′ = H) for comparative purposes. 4-Hydroxyquinoline-3-carboxylic acid (II; R = R′ = H) was first obtained by Camps (*Ber.*, 1901, **34**, 2703) by cyclisation of ethyl *o*-formamidophenylpropiolate; short trial of this method, however, convinced us that it was unlikely to prove attractive, because esterification of *o*-aminophenylpropiolic acid by alcoholic hydrogen chloride was apt to produce a considerable proportion of, apparently, 4-chloro-2-hydroxyquinoline (Baeyer and Bloem, *Ber.*, 1882, **15**, 2147), and attempted formylation of the ester, following the data supplied by Camps (*loc. cit.*), was unsuccessful.

The acid (II; R = R′ = H) has also been prepared by Gould and Jacobs (*J. Amer. Chem. Soc.*, 1939, **61**, 2890) by cyclisation of ethyl anilinomethylenemalonate (III; R = H) at 250°. It is not clear from their paper whether quinoline acids or their esters were in all cases obtained by this method, and fission of the primarily formed esters into ethylene and the acids would appear to be possible [cf. the pyrolytic conversion of alkyl acrylates and methacrylates into the acids (Ratchford, Rehberg, and Fisher, *J. Amer. Chem. Soc.*, 1944, **66**, 1864)]; our own results, however, discount this possibility.

The ester (III; R = H) is described by Claisen (*Annalen*, 1897, **297**, 1) as the sole product of the interaction of aniline and ethyl ethoxymethylenemalonate, and Gould and Jacobs presumably were able to reproduce this result, as they state that all condensations between the ethoxy-ester and various arylamines " went smoothly

and apparently in only one sense." Our own experience, however, was notably different. We were able to obtain no crystalline products by condensation of aniline or *p*-anisidine with the ethoxy-ester, and cyclisation of the crude materials led to mixtures. Thus the reaction using aniline gave three products, one of which was the expected *ethyl* 4-*hydroxyquinoline*-3-*carboxylate* (II; R = H; R′ = Et), identified by hydrolysis to the corresponding acid. A second substance, m. p. 318°, which gave analytical data in agreement with a formula $C_{15}H_{12}O_2N_2$ or $C_{16}H_{14}O_2N_2$, showed feebly acidic properties; it formed a crystalline sodium salt, but could not be hydrolysed in alkaline solution under ordinary conditions. The third component of the mixture was a *substance*, m. p. 118°, of formula $C_{18}H_{18}O_3N_2$. The reaction with *p*-anisidine gave rise to *ethyl* 4-*hydroxy*-6-*methoxyquinoline*-3-*carboxylate* (II; R = OMe; R′ = Et), readily hydrolysed to the *acid* (II; R = OMe; R′ = H), together with a *substance*, m. p. 133°, of formula $C_{20}H_{22}O_5N_2$.


(I.)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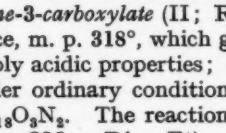
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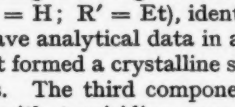
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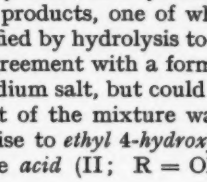
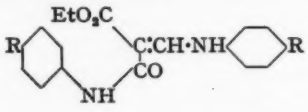

(V.)

The formulæ of the substances, m. p. 318°, 118°, and 133°, clearly indicate that two molecules of arylamine are involved. In view of the facility with which Michael-type additions of amines to unsaturated ketones occur (*e.g.*, Ruhemann and Watson, *J.*, 1904, **85**, 1170; Stewart and Pollard, *J. Amer. Chem. Soc.*, 1936, **58**, 1980; 1937, **59**, 2006, 2702; Cromwell *et al.*, *ibid.*, 1942, **64**, 2432; 1944, **66**, 872), analogous addition of arylamine to (III; R = H and OMe) or (IV; R = H and OMe) may be envisaged, and it may be significant that Surrey and Hammer (*ibid.*, 1946, **68**, 113) found that the yields of quinolines in the closely analogous synthesis from arylamines and oxaloacetic ester are diminished if the primary adduct contains free amine. Of the various possibilities which thus arise, the expression (V; R = H and OMe) [from (IV) by addition of arylamine and loss of alcohol] may be regarded as a tentative representation of the substances, m. p. 118° and 133°. An alternative explanation would be to formulate them as arylamidoarylaminomethyleneacetates (VI; R = H and OMe), isomeric with (V); the substance, m. p. 318°, would then be (VII). Each hypothesis is in conformity with the available evidence, and the second relates the substances, m. p. 118° and 318°, in a logical manner, although the analytical data for the second are not in good agreement with the formula, $C_{16}H_{12}O_2N_2$, of (VII). That (V) should survive the conditions of the reaction without loss of ethyl alcohol would not, perhaps, be anticipated, but this criticism would also apply to (VI), and no definite decision between these alternatives is possible at present.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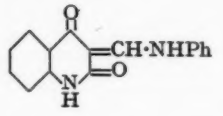
(VII.)

Experimental.

(Melting points are uncorrected.)

Products from Aniline and Ethyl Ethoxymethylenemalonate.—In our hands, the conditions of Claisen (*loc. cit.*) for the preparation of the ethoxy-ester always gave extremely poor yields, the main product being an undistillable resin (15 mm.), and we are much indebted to Professor A. R. Todd, F.R.S., for details of a reliable method based on that of Wheeler and Johns (*Amer. Chem. J.*, 1908, **40**, 233). The oil formed by heating the ethoxy-ester (10 g., b. p. 164—168°/17 mm.) and aniline (4·3 g.) for ½ hour on the steam-bath, after removal of alcohol (reduced pressure) was added during 5 minutes to liquid paraffin at 255—265° under nitrogen with stirring. After 20 minutes' heating, during which sublimation occurred, the turbid solution was cooled and filtered; the solid was digested with boiling ligroin (b. p. 60—80°) and crystallised (5 g.) from acetic acid (100 c.c.), giving *ethyl* 4-*hydroxyquinoline*-3-*carboxylate*, which formed dull needles, m. p. 275—276° (shrinking at 267°) from alcohol (Found: C, 66·2; H, 5·3; N, 6·4. $C_{13}H_{11}O_3N$ requires C, 66·3; H, 5·1; N, 6·45%); the ester was soluble in β-ethoxyethyl alcohol and *cyclo*hexanone in the hot, sparingly soluble in hot ethyl acetate and amyl formate, and insoluble in aqueous sodium bicarbonate. Hydrolysis on the steam-bath for ½ hour with aqueous sodium hydroxide (5%, 10 parts), followed by acidification, gave 4-hydroxyquinoline-3-carboxylic acid; the acid was easily soluble in aqueous sodium carbonate and bicarbonate, sparingly soluble in water and dilute hydrochloric acid, and formed colourless needles, m. p. 269—270° [efferv.; dependent on rate of heating; lit. m. ps., 266—267° (Camps), 267—268° (Gould and Jacobs)], from acetic acid (solubility in the hot, *ca.* 0·8%) (Found: C, 62·9; H, 3·5. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7%).

The acetic acid filtrate from the crude quinoline ester was evaporated (exhausted desiccator); the residue, after repeated digestion with alcohol and crystallisation from acetic acid, gave colourless hexagonal plates of the substance, m. p. 318—320° [Found (two samples): C, 71·75, 71·8; H, 4·6, 4·6; N, 10·9, 11·0. Calc. for $C_{16}H_{12}O_2N_2$: C, 72·7; H, 4·6; N, 10·6. Calc. for $C_{15}H_{12}O_2N_2$: C, 71·4; H, 4·8; N, 11·1. Calc. for $C_{16}H_{14}O_2N_2$: C, 72·1; H, 5·3; N, 10·5%]. The substance, which gave no ferric reaction, was almost insoluble in hydrochloric acid (dilute and concentrated), slightly soluble in aqueous sodium carbonate, and readily in warm aqueous sodium hydroxide, from which a colourless sodium salt separated on cooling. It was recovered unchanged after boiling with 10% sodium hydroxide for 3 hours under reflux, and was precipitated from alkaline solution at pH 9·5—10 (it could thus be separated from 4-hydroxyquinoline-3-carboxylic acid). It was only slightly attacked by acetic anhydride (3 hours under reflux; m. p. and mixed m. p. of product, 270—275°); reaction with phosphorus pentachloride–oxychloride mixture at 90° gave an oil which did not yield a crystalline product after condensation with aniline.

The original liquid paraffin filtrate and ligroin extracts deposited solid on standing; this was digested with hot ligroin (b. p. 40—60°), and crystallised from the same solvent, yielding long, faintly yellow needles of the *substance*, m. p. 118—119° (Found: C, 69·4; H, 5·75; N, 9·2. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·8; N, 9·0%), insoluble in hot aqueous

sodium carbonate, in cold aqueous sodium hydroxide, and in cold 2N-hydrochloric acid. Hydrolysis of the substance resulted when it was heated for ½ hour on the steam-bath with aqueous-alcoholic sodium hydroxide (5%; 40 parts), but the acid, m. p. 172—173° (efferv.), obtained on acidification was amorphous and seemed to decompose on attempted crystallisation from acetic acid.

Products from p-Anisidine and Ethyl Ethoxymethylenemalonate.—The oil obtained by heating *p*-anisidine (6·75 g.) and the ester (12 g.) for ½ hour on the steam-bath was freed from alcohol and added during 7—8 minutes to liquid paraffin as already described. After a total of 20 minutes, the mixture was cooled and filtered, and the solid, after digestion with boiling ligroin (b. p. 40—60°), crystallised from acetic acid, giving *ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate* (4·3 g.) as tiny straw-coloured prisms, m. p. 280—281° (Found: C, 62·85; H, 5·25. $C_{12}H_{13}O_4N$ requires C, 63·1; H, 5·3%). Hydrolysis was effected by heating the ester (2 g.) for 1 hour on the steam-bath with 5% aqueous sodium hydroxide (40 c.c.); *4-hydroxy-6-methoxyquinoline-3-carboxylic acid* (1·7 g.), obtained by acidification, was easily soluble in aqueous sodium bicarbonate, and very sparingly soluble in acetic acid, from which it formed almost colourless feathery needles, m. p. 278—279° (efferv.) (Found: C, 60·2; H, 4·2; N, 6·55. $C_{11}H_9O_4N$ requires C, 60·3; H, 4·1; N, 6·4%).

Digestion with ether of the solid which slowly separated from the liquid paraffin and ligroin filtrates gave material which, on crystallisation from alcohol, furnished lemon-yellow, prismatic needles of the *substance*, m. p. 132—133° (1·85 g.) (Found: C, 64·6; H, 6·0; N, 8·0. $C_{20}H_{22}O_5N_2$ requires C, 64·85; H, 6·0; N, 7·6%). This substance, which was insoluble in cold sodium hydroxide, was hydrolysed by heating it (0·5 g.) for 1 hour on the steam-bath with 10% aqueous sodium hydroxide (3 c.c.), alcohol (10 c.c.), and water (3 c.c., added after ½ hour). Dilution with water and ether-extraction gave an oil, acetylation of which yielded acet-*p*-anisidide (0·15 g.), m. p. and mixed m. p. 126—128°. Acidification of the alkaline solution after ether-extraction gave an amorphous acid (70 mg.), m. p. 174—177° (efferv.), which yielded only traces of crystalline material on attempted esterification (alcoholic sulphuric acid). In another similar hydrolysis of the substance, m. p. 133°, the acid fraction had m. p. 198—200°, and was either insoluble in, or decomposed on attempted crystallisation from, numerous solvents.

Grateful acknowledgement is made of financial and other support from Imperial Chemical Industries Limited (Dyestuffs Division), of a grant from the Research Fund of the Council of the Durham Colleges, and of financial assistance during the later stages of the work from the Medical Research Council.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.
WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

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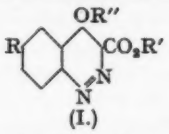
227. *Cinnolines. Part VIII. Esters of 4-Hydroxy-cinnoline- and -quinoline-3-carboxylic Acids.*

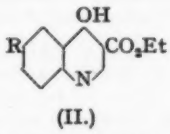
By J. C. E. SIMPSON.

The preparation and properties of ethyl esters of 4-hydroxy-cinnoline- and -quinoline-3-carboxylic acids are described.

FOR the purpose of investigating the properties of functional derivatives of 4-hydroxycinnoline-3-carboxylic acid (I; R = R′ = R″ = H), obvious advantages would attend the development of a practical method of selectively substituting either the carboxyl or the hydroxyl group. Earlier experiments in this direction (Schofield and Simpson, *J.*, 1945, 512) were not successful, but it has now been found that the *esters* (I; R = H and OMe; R′ = Et; R″ = H) can be prepared in about 25% yield by esterification of the corresponding acids with alcohol and either 100% sulphuric acid or 20% oleum (cf. Newman, *J. Amer. Chem. Soc.*, 1941, **63**, 2431; Baxter and Spring, *J.*, 1945, 232). Application of the same method to the appropriate quinoline acids gave about 15% of the corresponding esters (II; R = H and OMe), identical with those prepared by pyrolysis of ethyl arylaminomethylenemalonates (preceding paper).



(I.)



(II.)

These cinnoline and quinoline esters are all readily hydrolysed to the parent acids, but are sharply differentiated in other respects. Thus the cinnoline esters, in contrast to the quinoline analogues, are appreciably acidic. Further, whereas the cinnoline derivatives were readily acetylated to yield (I; R = H and OMe; R′ = Et; R″ = Ac), similar treatment of the esters (II; R = H and OMe) was without effect; (II; R = H) also resisted more drastic treatment, but (II; R = OMe) was slowly converted under these conditions into the 4-*acetoxy*-derivative.

The contrast between the facile acetylation of the cinnoline hydroxy-esters and the resistance of the analogous quinoline derivatives is in harmony with the general behaviour, in this respect, of 4-hydroxy-compounds in the two heterocyclic series, although no really clear-cut conclusions regarding the latter group can be drawn from the somewhat confused literature on the subject. A more detailed discussion of this point, and of its theoretical implications, is reserved for a future communication.

EXPERIMENTAL.

(Melting points are uncorrected.)

Preparation of Esters.—The cinnoline acids were crude and used without further purification (Schofield and Simpson, *loc. cit.*); the quinoline acids were purified by crystallisation from, or digestion with, acetic acid. The general esterific

ation procedure followed those of Newman and of Baxter and Spring (*locc. cit.*), the finely-powdered acid (1 part) being dissolved in 20% oleum (5—7 parts by volume) with cooling, and the solution so obtained added to absolute alcohol (20—30 parts by volume). After 15—20 minutes' heating on the steam-bath, the mixtures were cooled, poured into excess of aqueous sodium carbonate, acidified with acetic acid, and then neutralised with sodium bicarbonate solution. (To ensure separation from unchanged acid, the solutions containing the quinoline esters were finally made alkaline with sodium carbonate, but in the case of the cinnoline esters alkalinity was avoided because of their acidic nature.) Alcohol was driven off, and the solid which had separated was filtered cold and washed with water. All the hydroxy-esters, and also 4-hydroxycinnoline, gave reddish colorations with ferric chloride (cf. Camps, *Ber.*, 1901, **34**, 2703); the derived acetoxy-esters gave negative reactions.

Quinoline Esters.—Ethyl 4-hydroxyquinoline-3-carboxylate (yield, 0·15 g. from 1 g. of acid) crystallised from acetic acid in soft, colourless needles, m. p. 275—276° alone and when mixed with the sample described in the preceding paper; all samples showed some shrinking at about 240°. Unesterified acid (0·7 g., identified by m. p. and mixed m. p.) was recovered from the alkaline mother-liquor. Unchanged ester was the sole product after it (100 mg.) had been heated at 95° for 2½ hours with 1 c.c. of a mixture of pyridine (1 c.c.) and acetic anhydride (1·5 c.c.), as also after 1 hour's refluxing of its suspension in acetic anhydride (15 parts) (solvent removed and total residue examined).

Ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (yield, 15%) had m. p. 280—281° alone and mixed with an authentic sample (preceding paper) after crystallisation from aqueous acetic acid. The original alkaline filtrate yielded 40% of unesterified acid. The solubility of the ester in boiling 3% aqueous sodium bicarbonate (*ca.* 0·1%) was several times greater than in boiling water, but the product which separated from the alkaline solution was slightly impure ester and not a sodium salt. This behaviour appears to indicate very weakly acidic properties for the compound, which, however, is sharply differentiated from the cinnoline esters (below). The ester was unaffected by a mixture of pyridine and acetic anhydride at 95°, but when it (0·5 g.) was refluxed with acetic anhydride (6 c.c.), a clear solution resulted after 3 hours. After a further 2 hours' refluxing, solvent was removed (evacuated desiccator); a solution of the residue in hot ligroin (b. p. 60—80°), after filtration from a little insoluble matter, deposited *ethyl 4-acetoxy-6-methoxyquinoline-3-carboxylate*, which formed long, silky, colourless needles, m. p. 124—125°, from benzene–ligroin (b. p. 60—80°) (Found: C, 62·3; H, 5·2; N, 4·9. $C_{15}H_{13}O_5N$ requires C, 62·3; H, 5·2; N, 4·8%).

Cinnoline Esters.—*Ethyl 4-hydroxycinnoline-3-carboxylate* was sparingly soluble in hot water and crystallised in long, silky, colourless needles, m. p. 191—192° after previous shrinking (Found: C, 60·7; H, 4·6; N, 13·35. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%). It dissolved easily in hot alcohol and in warm aqueous sodium bicarbonate (for this reason it was sometimes isolated in part as the sodium salt, m. p. 229—230°, converted into the free ester by very dilute hydrochloric acid). 2 G. of acid yielded 0·35 g. of ester, 0·35 g. of pure unchanged acid, and 0·32 g. of a mixture (presumed ester and acid); from 1 g., 0·55 g. of a mixture of ester and sodium salt was obtained. The use of 100% sulphuric acid instead of 20% oleum gave essentially similar results. When the ester was refluxed with hydrochloric acid (5N, 40 parts), it was rapidly and quantitatively hydrolysed to the parent acid, identified by m. p. and mixed m. p. *Ethyl 4-acetoxycinnoline-3-carboxylate* (yield, 80%) was formed when the ester was either refluxed with acetic anhydride (5 parts) or heated with 10 parts of a mixture of pyridine and the anhydride (2 : 3) for ½ hour at 95°. Removal of the solvent in an evacuated desiccator left an oil which crystallised on trituration with a little water. The acetoxy-ester formed long colourless needles, m. p. 82—83°, from aqueous alcohol [Found: C, 59·75; H, 4·6; N (mean of three), 11·55. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·65; N, 10·8%]; it was extremely soluble in alcohol, and insoluble in aqueous sodium bicarbonate. It dissolved slowly in cold 4N-ammonia, and underwent selective hydrolysis of the 4-acetoxy-group when warmed for 5 minutes at 95° with 0·4N-ammonia (30 parts), the hydroxy-ester (identified by m. p. and mixed m. p.) crystallising as the sole product when the solution was acidified with acetic acid.

Ethyl 4-hydroxy-6-methoxycinnoline-3-carboxylate, very sparingly soluble in hot water, formed soft, almost colourless, flattened needles, m. p. 233—234°, from aqueous acetic acid (Found: C, 57·5; H, 5·0; N, 11·65. $C_{12}H_{12}O_4N_2$ requires C, 58·0; H, 4·9; N, 11·3%), and, like its analogue, was soluble in warm aqueous sodium bicarbonate. Hydrolysis with boiling 2N-hydrochloric acid regenerated the parent acid (m. p. and mixed m. p.). When the ester was heated at 95° for ½ hour with 20 parts of a mixture of pyridine and acetic anhydride (2 : 3), a crystalline residue of *ethyl 4-acetoxy-6-methoxycinnoline-3-carboxylate* was formed after removal of solvents in an evacuated desiccator; this substance crystallised from alcohol in long, pale saffron-coloured brittle rods, m. p. 152—153° (Found: C, 57·6; H, 5·15; N, 10·1. $C_{14}H_{14}O_5N_2$ requires C, 57·9; H, 4·85; N, 9·65%), and, like its methoxyl-free analogue, was quantitatively hydrolysed to the parent hydroxy-ester when warmed for a few minutes with dilute ammonia, the product being isolated by addition of acetic acid, and identified by m. p. and mixed m. p.

Grateful acknowledgment is made of facilities afforded by Imperial Chemical Industries Limited (Dyestuffs Division) in connexion with this investigation, and of financial support from the Medical Research Council.

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228. *The Mechanism of the Bucherer Reaction. Part I. The Kinetics of the Conversion of Naphthylamines into Naphthols.*

By W. A. COWDREY and C. N. HINSHELWOOD.

The kinetics of the Bucherer reaction for the conversion of naphthylamine derivatives into the corresponding naphthols have been elucidated. 4-Amino-, 5-amino-, and 5-dimethylamino-naphthalene-1-sulphonic acids all combine with sodium bisulphite during the rate-determining stage of the reaction by a bimolecular process which is of first order with respect to both naphthylamine derivative and bisulphite. The rates and energies of activation of the reactions have been determined. The manner in which the velocity varies with pH of the reaction medium indicates that the naphthylaminesulphonate ion, $C_{10}H_6(NR_2)\cdot SO_3^-$, and bisulphite ion are the reactant forms.

The mechanism of the reaction is discussed in the light of the observed kinetics, and it is suggested that addition of bisulphite to α-naphthylamines takes place directly at the C–C double bond.

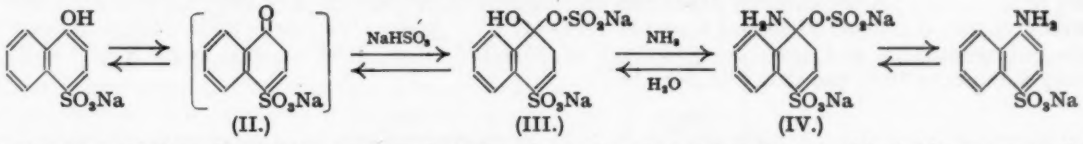
THE unusual catalytic effect of sulphites in the interconversion of naphthylamine and naphthol derivatives was first observed by Lepetit (Pli cacheté Nr. 888, May 16, 1896; *Bull. Soc. Mulhouse*, 1903, 326; see also

Ber., 1921, **54**, 620), who found that naphthionic acid could readily be converted into 1-naphthol-4-sulphonic acid by heating with aqueous sodium bisulphite. Bucherer (*J. pr. Chem.*, 1904, **69**, 49) subsequently demonstrated the more general nature of the reaction and showed that it was reversible, in the sense that naphthols heated with aqueous solutions of amines and amine sulphites yield naphthylamines. The reaction is of considerable technical importance in that it provides a means of converting α-naphthylamine compounds (available *via* α-nitronaphthalene) into α-naphthols, or β-naphthol derivatives (obtained from β-naphthalenesulphonic acid) into β-naphthylamines and *N*-substituted β-naphthylamines. Detailed summaries and bibliographies of the reaction are given in Thorpe's " Dictionary of Applied Chemistry," 1922, Vol. IV, p. 415, and in " Organic Reactions " (Adams), Vol. I, p. 105.

There has been considerable speculation regarding the mechanism of this reaction. Bucherer showed that a very soluble intermediate bisulphite compound is formed, stable to acid but readily hydrolysed by alkali to the corresponding naphthol. This he thought was the naphthyl hydrogen sulphite (I), and therefore formulated the mechanism :

$$\underset{R\cdot NH_2}{\text{Naphthylamine}} \underset{NH_3}{\overset{NaHSO_3}{\rightleftharpoons}} \underset{R\cdot O\cdot SO\cdot OH \quad (I.)}{\text{Naphthyl hydrogen sulphite}} \underset{NaHSO_3}{\overset{Alkali}{\rightleftharpoons}} \underset{R\cdot OH}{\text{Naphthol}}$$

Woroshtzow (*J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1669) suggested that the compound was a derivative of the keto-form of the naphthol (II), and he assigned to it structure (III). Fuchs and Stix (*Ber.*, 1922, **55**, 662) postulated a further bisulphite compound (IV) derived from the naphthylamine, and they advanced for the conversion of a naphthol into a naphthylamine the following type of mechanism :



The structure of these bisulphite compounds is based on the assumption that the bisulphite compound of a ketone has the structure $R_2C(OH)\cdot O\cdot SO\cdot ONa$, but more recently Raschig and Prahl (*Annalen*, 1926, **448**, 265) have shown that the correct structure is in fact $R_2C(OH)\cdot SO_3Na$. Thus the above structures (III) and (IV) require to be corrected to (V) and (VI) respectively.

The evidence for the Fuchs and Stix type of mechanism is based largely on the fact that bisulphite compounds can be isolated from naphthols, and by analogy with the properties of simple aldehyde-bisulphite compounds these would be expected readily to react with ammonia to yield bisulphite compounds analogous to (VI) (cf. Raschig, *Ber.*, 1926, **59**, 859). No serious attempt has been made to determine the kinetics of the reaction in either direction. Kogan and Nikolaeva (*J. Appl. Chem. U.S.S.R.*, **11**, 653) did follow the progress of the conversion of 5-aminonaphthalene-1-sulphonic acid into the corresponding naphthol by the rate at which ammonium ion was formed, but they attempted no mathematical analysis of their results. The present series of papers describes a systematic study of the kinetics of the Bucherer reaction in both directions designed to obtain more fundamental information about the mechanism.

The conversion of naphthylamines into naphthols was first investigated, the original reaction of Lepetit for the conversion of naphthionic into 1-naphthol-4-sulphonic acid being selected as the most suitable example. Naphthionic acid is precipitated almost quantitatively from solutions of its salts by addition of strong acid, and this provides a convenient and accurate method for following the reaction. It became apparent during the course of this work that the bisulphite compounds formed during the reaction did not react with iodine in acid solution, and this enabled the concentrations both of free and of combined bisulphite to be determined throughout the course of the reaction by iodine titration. The reaction was studied in the presence of a large excess of a buffer solution in order to avoid changes in pH which would seriously interfere with the interpretation of the results.

Under these conditions the initial rate of reaction was directly proportional to the product of the concentrations of naphthionate and bisulphite over quite a wide range of each (see Table I). Moreover, at temperatures between 60° and 100° in presence of a large excess of bisulphite (about 4 mols.) the falls in molar concentrations of naphthionate and bisulphite were parallel, so that the progress of the reaction over substantially the whole of its course could be expressed accurately by the usual formula for a bimolecular process, *viz.*,

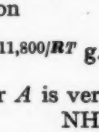
$$k_2 t = \frac{1}{(a-b)} \ln \frac{b(a-x)}{a(b-x)}$$

where a and b are the initial concentrations of bisulphite and naphthionate respectively, and x the fall in naphthionate or bisulphite or the rise in ammonium-ion concentration after a time t. On increasing the

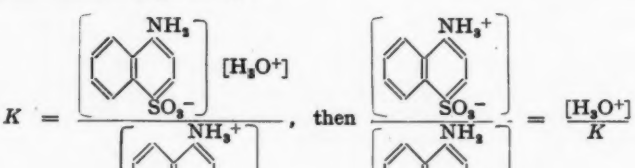
temperature to 120° the fall in bisulphite concentration became significantly less than that of naphthionate, owing to subsequent partial dissociation of the bisulphite compound into naphthol and bisulphite. Under these conditions the method of analysing the results required modification, because the concentration of bisulphite at a time t was not accurately given by $(a - x)$. This was allowed for by calculating the pseudo-unimolecular constant (k_1) for various reaction times, assuming the constancy of the bisulphite concentration, and then dividing these k_1 values by the mean bisulphite concentrations over the same time period to obtain the true bimolecular constant k_2. The mean bisulphite concentrations were estimated from the observed variation in bisulphite concentration with time by graphical integration.

The plot of log k_2 against $1/T$ for temperatures from 60° to 120° c., where T is the absolute temperature, was linear, with a slope corresponding to 11,800 cals. per g.-mol. for the energy of activation. The velocity of the reaction could thus be expressed by the equation

$$k_2 = 4{\cdot}3 \times 10^2 e^{-11{,}800/RT} \text{ g.-mol.}^{-1} \text{ l. sec.}^{-1}$$

This value of $4{\cdot}3 \times 10^2$ for the pre-exponential factor A is very low, but it is not inconsistent with the view that reaction occurs between ions of like charge, *e.g.*,  and HSO_3^- (cf. Bell., *J.*, 1943, 629).

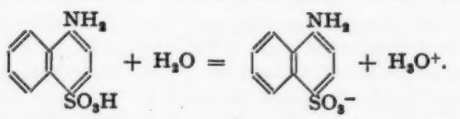
The nature of the ionic species participating in the process was investigated by carrying out the reaction in a range of buffers, and observing the variation of the rate with pH. With sodium acetate–acetic acid buffers which have a pH not seriously dependent on temperature between 25° and 100°, the rate was observed to be only slightly decreased on passing from pH 3·5 to pH 4·4. Making the assumptions that the dissociation constant of naphthionic acid, given by Ebersbach (*Z. physikal. Chem.*, 1893, **11**, 624) as $2{\cdot}0 \times 10^{-3}$ at 25°, is not very different at 100°, and that it is given by :



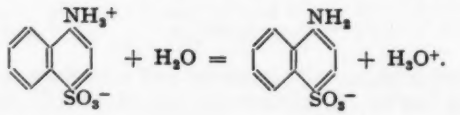
The ratio of $R{\cdot}NH_3^+$ to $R{\cdot}NH_2$ should thus vary from 0·16 at pH 3·5 to 0·02 at pH 4·4, so that over this range the concentration of $R{\cdot}NH_3^+$ changes markedly whilst that of $R{\cdot}NH_2$ is not seriously affected. Since the rate is insensitive to pH in this range it follows that it is the free base $R{\cdot}NH_2$ and not its conjugate acid $R{\cdot}NH_3^+$ which reacts. The pH range was extended to 6·9 using sodium hydroxide–potassium dihydrogen phosphate buffers (for which, unfortunately, no information has been found for the change of pH between 25° and 100°), and the variation in rate of reaction at 100° with pH at 20° is shown in the Fig. The dotted line shows the calculated variation of rate with pH assuming that HSO_3^- is the reactant form of the sulphite, and further that the pH of the buffers and the second dissociation constant of sulphurous acid ($5{\cdot}0 \times 10^{-6}$ at 25°) do not change seriously between 25° and 100°. These assumptions are only rough approximations, and the measure of agreement between observed and calculated values affords reasonable support for the HSO_3^- mechanism.

Similar but less detailed investigations have also been carried out on the hydrolyses of 5-amino- and 5-dimethylamino-naphthalene-1-sulphonic acids to 1-naphthol-5-sulphonic acid. The kinetics of the reactions of both substances were formally the same as those of the naphthionic acid reaction. For 5-aminonaphthalene-1-sulphonic acid the rate at 100° was about 1/6th of that of naphthionic acid, the energy of activation 13,700 cals. per g.-mol., and the pre-exponential factor $9{\cdot}7 \times 10^2$ g.-mol.$^{-1}$ l. sec.$^{-1}$, whilst for the di-*N*-methylated derivative the corresponding values were 1/34th, 18,300 cals. per g.-mol. and $2{\cdot}9 \times 10^5$ g.-mol.$^{-1}$ l. sec.$^{-1}$. Further work on a series of nuclear-substituted naphthylaminesulphonic acids would be of interest in correlating

* Ebersbach gives this value for the dissociation constant assuming it refers to the equation

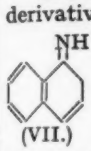


Obviously, however, the sulphonic acid grouping is completely ionised in aqueous solution, and the results actually refer to the reaction :

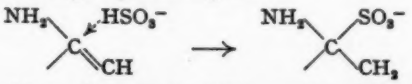


structure with rate of reaction and energy of activation, but so far it has not been possible to prepare the necessary naphthalene compounds.

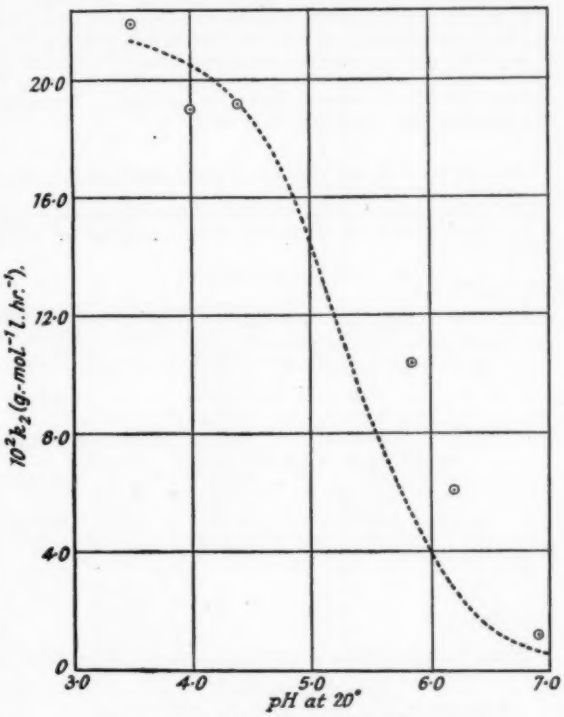
Meanwhile the fact that the di-*N*-methylated derivative undergoes the bisulphite hydrolysis by a process kinetically similar to that of the unmethylated compound is informative regarding the way in which the bisulphite ion combines with the naphthylamine. Clearly, the dimethylamino-compound cannot form an aminosulphinic acid $R{\cdot}NH{\cdot}SO_2H$ similar to the sulphurous ester of the naphthol put forward by Bucherer, nor can it react in an imino-form (VII) analogous to the keto-form suggested by Woroshtzow. More probably the bisulphite ion first attaches itself to the carbon atom attached to the amino-group, the resultant carbanion then picking up a proton and the sulphonic acid group ionising thus :



(VII.)



This would result in 1 : 2-addition of bisulphite, yielding the same compound as postulated in the Fuchs and Stix mechanism. The possibility of 1 : 4-addition, however, cannot be excluded. This type of direct addition of bisulphite to C=C linkages is known, *e.g.*, acraldehyde adds two molecules of bisulphite, one to the C=O and the other to the C=C linkage (Rosenthal, *Annalen*, 1886, **233**, 36). It has also been suggested by Fuchs and Stix to account for the mode of attachment of the second molecule of bisulphite to 1 : 5-dihydroxynaphthalene (*Ber.*, 1922, **55**, 658).



Variation of rate with pH.

Experimental.

Materials.—Sodium naphthionate was prepared from commercial naphthionic acid, and repeatedly recrystallised from water. 5-Aminonaphthalene-1-sulphonic acid (Laurent acid) was obtained commercially and purified by acetylation and recrystallisation of the *p*-toluidine salt of its acetyl derivative (cf. Forster, Harrison, and Watson, *J. Soc. Chem. Ind.*, 1928, **47**, 155). 5-Dimethylaminonaphthalene-1-sulphonic acid was prepared by Dr. R. H. Wilson from purified Laurent acid by methylation with methyl sulphate and sodium hydroxide in aqueous solution.

Kinetic Measurements with Naphthionic Acid.—For carrying out reactions at pH 4·2 solutions were prepared 0·5M in acetic acid and 0·2M in sodium acetate and containing the required concentration of sodium bisulphite. The ionic

Table I.

Initial Rates of Reaction at 100° *with Various Concentrations of Naphthionate and Bisulphite.*
(*Buffer pH* 4·2 *at* 20°.)

Initial concentrations. [Naphthionate].	[Bisulphite].	Initial velocity, g.-mol./l./hr.	Initial velocity / [Naphthionate][Bisulphite]
0·154	0·150	0·0040	0·17
0·154	0·300	0·0080	0·17
0·075	0·150	0·0021	0·18
0·0375	0·150	0·0011	0·19
0·0363	0·300	0·0026	0·24
0·0348	0·450	0·0038	0·24

Table II.

Comparison of the Rates of Naphthionate Disappearance and Ammonium Ion Appearance at 100°.
(Initially 0·30M-bisulphite and 0·035M-naphthionate.)

Time (hours).	[Naphthionate].	[NH_4].	[NH_4] + [Naphthionate].
1·0	0·0352	0·0026	0·0378
3·0	0·0310	0·0068	0·0378
6·0	0·0252	0·0127	0·0379
10·0	0·0199	0·0179	0·0378
18·0	0·0121	0·0255	0·0376
24·0	0·0078	0·0296	0·0374
37·0	0·0028	0·0340	0·0368

These results show that no significant amount of naphthionic acid is converted into 4 : 4′-dinaphthylamine-1 : 1′-disulphonic acid.

strength of these solutions was kept constant by addition of sodium chloride. Sodium naphthionate (1·000 g.) was accurately weighed into soft-glass tubes, a measured quantity of the bisulphite–buffer solution was added, and the air was displaced to prevent oxidation of the bisulphite. The tubes were sealed and heated for known times in baths at the various temperatures. To stop the reaction the tubes were cooled rapidly in cold water; unchanged naphthionic acid was then precipitated by addition of concentrated hydrochloric acid (2 c.c.). After 30 minutes to complete the precipitation, the naphthionic acid was filtered off on a sintered-glass crucible, washed with water (10 c.c.), dried at 90°, and weighed. Ammonium ion was estimated in the filtrate by the usual Kjeldahl method. A separate series of tubes was used to follow the change in bisulphite concentration by titration with N/10-iodine in strongly acid solution. Concentrations are expressed as g.-mol./l.

More accurate determination of bimolecular constants.

(Two values are given for the bisulphite concentration, the one as determined by iodine titration, the other expressed as $a - x$ calculated as the difference between the initial bisulphite concentration, a, and the concentration of naphthionate reacted, x.)

(i) At 60·6°.

t (hours).	[Naphthionate] $(b - x)$.	[Bisulphite] (actual).	[Bisulphite] $(a - x)$.	10^2k_2 (g.-mol.$^{-1}$ l. hr.$^{-1}$).
0·0	0·0767	0·285	0·285	—
5·0	0·0736	—	0·282	2·94
10·0	0·0709	0·280	0·279	2·76
18·0	0·0661	—	0·274	2·92
41·5	0·0553	0·264	0·263	2·86
64·0	0·0469	—	0·255	2·86
91·5	0·0379	0·245	0·246	2·93
115·5	0·0317	—	0·240	2·96
143·0	0·0270	0·227	0·235	2·86
188·0	0·0192	0·227	0·227	2·96

Average $k_2 = 2·90 \times 10^{-2}$

(ii) At 120·2°.

(Here the integrated mean bisulphite concentrations are given instead of those calculated as $a - x$.)

t (hours).	[Naphthionate] $(b - x)$.	k_1, hrs.$^{-1}$.	[Bisulphite] (actual).	[Bisulphite] (integ. mean).	10^2k_2 (g.-mol.$^{-1}$ l. hr.$^{-1}$).
0·00	0·0740	0·115	0·291	0·291	—
0·50	0·0699	0·112	—	0·289	39·8
2·00	0·0591	0·121	0·276	0·283	39·6
2·50	0·0546	0·120	—	0·282	42·9
3·50	0·0486	0·120	0·268	0·280	42·6
4·50	0·0436	0·117	—	0·277	42·2
6·00	0·0377	0·113	0·259	0·273	41·4
7·50	0·0323	0·111	—	0·267	41·9
9·50	0·0241	0·118	0·253	0·265	44·1
11·50	0·0193	0·117	0·253	0·264	44·3

Average $k_2 = 42·1 \times 10^{-2}$

The average bimolecular rate constants (g.-mol.$^{-1}$ l. hr.$^{-1}$) at intermediate temperatures were $8·52 \times 10^{-2}$ at 80·5° and $19·1 \times 10^{-2}$ at 99·8°.

Variation in the velocity with pH. A series of buffer solutions was prepared, each approximately 0·15M in total sulphite, and having pH's varying from 3·5 to 6·9 at 20°. For buffers of pH 3·5—4·4 acetic acid–sodium acetate mixtures were used, sodium hydroxide–potassium dihydrogen phosphate combinations being employed for the remainder. Velocity determinations were carried out by adding the bisulphite–buffer solution (40 c.c.) to sodium naphthionate (1·000 g.) and heating the mixture in sealed tubes at 100°. In all cases the buffer solution was in large excess over that of the naphthionate, so that no serious pH change occurred from formation of ammonia during the course of the reaction.

The variation of the bimolecular velocity constant at 100° with the pH of the reaction mixture (measured with a glass electrode at 20°) was as follows:

pH	3·5	4·0	4·4	5·8	6·2	6·9
10^2k_2 (g.-mol.$^{-1}$ l./hr.$^{-1}$)	21·9	19·0	19·2	10·4	6·1	1·25

The figure shows these values along with the calculated plot (dotted line), the bisulphite ion being assumed to be the reactive species. The latter was obtained from the relationship

$$[HSO_3^-] = \frac{T}{1 + K_D/[H_3O^+]}$$

where T is the total sulphite concentration, $[HSO_3^-] + [SO_3^{--}]$, and K_D is the second dissociation constant of sulphurous acid at 25°.

Kinetic measurements with 5-aminonaphthalene-1-sulphonic acid. A set of rate determinations was carried out in buffer pH 4·2 at various temperatures as already described above for naphthionic acid. In this case, however, free 5-aminonaphthalene-1-sulphonic acid (0·800 g.) was used in place of sodium naphthionate, and to compensate for this the buffer was prepared 0·472M in acetic acid and 0·278M in sodium acetate.

At 80·0°.

t (hours).	[Laurent acid] $(b - x)$.	[Bisulphite] (actual).	[Bisulphite] $(a - x)$.	10^2k_2 (g.-mol.$^{-1}$ l./hr.$^{-1}$).
0·0	0·0809	0·292	0·292	—
24·0	0·0751	—	0·286	1·06
65·5	0·0654	0·273	0·276	1·13
69·0	0·0647	—	0·276	1·15
97·0	0·0558	0·270	0·270	1·20
119·0	0·0540	—	0·263	1·22
168·0	0·0470	0·258	0·258	1·18
217·5	0·0410	—	0·252	1·16
263·5	0·0354	0·249	0·246	1·18
365·5	0·0264	—	0·237	1·18
452·5	0·0204	—	0·231	1·20

Average $k_2 = 1·17 \times 10^{-2}$

The average bimolecular rate constants at higher temperatures were $3·44 \times 10^{-2}$ at 99·9° and $8·68 \times 10^{-2}$ at 120·2°.

Kinetic measurements with 5-dimethylaminonaphthalene-1-sulphonic acid. These measurements were carried out as described for Laurent acid above, using 0·900 g. of free dimethylaminonaphthalene-1-sulphonic acid per tube.

At 120·0°.

t (hours).	[Dimethyl-L-acid] $(b - x)$.	[Bisulphite] (actual).	[Bisulphite] $(a - x)$.	10^2k_2 (g.-mol.$^{-1}$ l./hr.$^{-1}$).
0·0	0·0842	0·300	0·300	—
21·0	0·0744	—	0·290	1·98
39·2	0·0667	0·270	0·283	1·94
63·7	0·0564	—	0·272	2·20
79·0	0·0560	0·255	0·272	1·82
94·7	0·0445	—	0·261	2·45
117·0	0·0432	0·244	0·259	2·06
171·5	0·0313	—	0·252	2·20
221·2	0·0191	0·237	0·235	2·59

Average $k_2 = 2·15 \times 10^{-2}$

The average bimolecular rate constants were $0·64 \times 10^{-2}$ at 99·9° and $6·3 \times 10^{-2}$ at 138·0°.

Thanks are due to the Dyestuffs Division of Imperial Chemical Industries Limited for facilities to one of us (W. A. C.) which have enabled him to take part in this work and that recorded in the following Parts II, III, and IV.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, March 30th,* 1946.]

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229. *The Mechanism of the Bucherer Reaction. Part II. Isolation of Bisulphite Compounds from Naphthionic Acid.*

By W. A. COWDREY.

The product of the reaction between naphthionic acid and sodium bisulphite has been isolated and separated into two pure compounds.

The major constituent, $C_{20}H_{24}O_{16}NS_4Na_3$, appears to be the *tetrahydrate* of the di-bisulphite compound of 4 : 4′-dinaphthylamine-1 : 1′-disulphonic acid (A). The connection between this substance and its simple analogue, iminomethanesulphonic acid, prepared from the formaldehyde-bisulphite compound and ammonia by Raschig, is discussed, and its formation is correlated with the common occurrence of dinaphthylamines as by-products in the Bucherer reaction.

The other *compound*, $C_{10}H_{10}NS_2Na,1\frac{1}{2}H_2O$, is either the monosodium salt of the bisulphite compound of naphthionic acid (IV), or the sodium ammonium salt of the bisulphite compound of 1-naphthol-4-sulphonic acid (V).

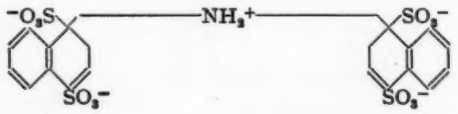
A detailed scheme for the mechanism of the Bucherer reaction as applied to the conversion of naphthylamines into naphthols is proposed, based on this work and the kinetic study reported in Part I.

As early as 1904 Bucherer showed that very soluble bisulphite compounds were formed during the reaction between naphthylamine derivatives and sodium bisulphite, but few such substances have as yet been isolated in a pure condition from simple monohydroxy- or monoamino-naphthalene derivatives, and directions given for their preparation are often vague (cf. Woroshtzow, *Ann. Chim.*, 1917, **7**, 50). The compounds which Bucherer himself prepared (*J. pr. Chem.*, 1904, **69**, 80) were not isolated pure and no analytical examination of them is reported (see Friendländer, *Ber.*, 1921, **54**, 620). Fuchs and his co-workers describe the preparation and analysis of bisulphite compounds from a number of aminonaphthols and polyhydroxy-naphthalene and -benzene derivatives (*Ber.*, 1921, **54**, 245; 1922, **55**, 658; 1920, **53**, 886), but the majority of these are necessarily complex and some of them do not correspond to the intermediates formed in the Bucherer process because they are not completely hydrolysed to the parent substance by alkali.

A notable exception in this connection appeared to be the compound described by Woroshtzow (*Ber.*, 1929, **62**, 57) from 2-naphthol-1-sulphonic acid, but on repetition this work has been found incorrect. Purified 2-naphthol-1-sulphonic acid, when converted into its disodium salt and treated with sulphur dioxide in concentrated aqueous solution, does not in fact yield a crystalline bisulphite compound in the manner described. The method outlined by Woroshtzow for preparing sodium 2-naphthol-1-sulphonate by sulphonating β-naphthol actually gives mainly the 2-naphthol-6-sulphonate. This forms a very soluble disodium salt, and a sparingly soluble monosodium salt which reacts with iodine in neutral or alkaline solution and was probably mistaken for a bisulphite compound.

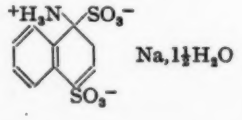
The kinetic investigation described in Part I showed that a bisulphite compound was formed during the rate-determining stage of the reaction between sodium naphthionate and sodium bisulphite which was stable in presence of excess of bisulphite below 100°. The precise nature of this substance, and in particular whether it still contains any of the original nitrogen, has never been established, although it is made regularly on an industrial scale as an intermediate in the conversion of naphthionic acid into 1-naphthol-4-sulphonic acid (cf. D.R.-P. 109,102; U.S.P. 1,880,701). From the mechanism suggested by Fuchs and Stix (see Part I) the product of the reaction would be expected to consist of a mixture of naphthylamine- and naphthol-bisulphite compounds, and this investigation was carried out to obtain more definite information about the composition of the equilibrium mixture.

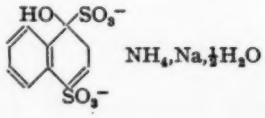
It was found that the reaction product freed from inorganic salts could be separated into a mixture of two substances, both of which have been prepared in a pure condition. The main *constituent* (A) crystallises in colourless spherulites and has the composition $C_{20}H_{24}O_{16}NS_4Na_3$. It is soluble in about its own weight of water but almost insoluble in organic solvents, and it does not react with acidified iodine. On boiling with aqueous sodium hydroxide the whole of its nitrogen is evolved as ammonia, and at the same time half of its sulphur becomes available as sulphite. It is almost certainly the di-bisulphite compound of the dinaphthylamine derivative with the following structure:



$Na_3,4H_2O$ (A)

The other *compound* (B) separates in crystals of the anorthic system having the form of four-sided prisms terminated by four-faced truncated pyramids, with a composition corresponding to $C_{10}H_{13}O_{7\cdot5}NS_2Na$, *i.e.*, $C_{10}H_{10}O_6NS_2Na,1\frac{1}{2}H_2O$. Its properties are very similar to those of (A). Two structures are possible for this compound on the available evidence, *viz.*,



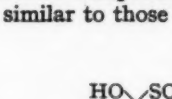
$Na,1\frac{1}{2}H_2O$ and


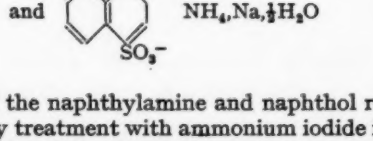
$NH_4,Na,\frac{1}{2}H_2O$ (B)

which correspond to the bisulphite compounds of the naphthylamine and naphthol respectively. Compound (A) can, moreover, readily be converted into (B) by treatment with ammonium iodide in concentrated aqueous-alcoholic solution, even in presence of strong acid. This means either that the sodium ammonium salt of the naphthol bisulphite compound is rather more sparingly soluble and separates in preference to the disodium or diammonium salt, or alternatively but less probably that compound (A) actually reacts with ammonium ion to form the naphthylamine bisulphite compound. So far it has not been possible to decide definitely between the two possible structures for compound (B).

Concerning the formation of compound (A), it is of interest to recall Raschig and Prahl's work (*Ber.*, 1926, **59**, 859; *Annalen*, 1926, **448**, 265) on the reaction between the formaldehyde-bisulphite compound (I) and ammonia in connection with the mechanism of the Bucherer reaction. Below 10° the main product was aminomethanesulphonic acid (II), but above this temperature the iminomethanesulphonate (III) was chiefly formed.

(I.)

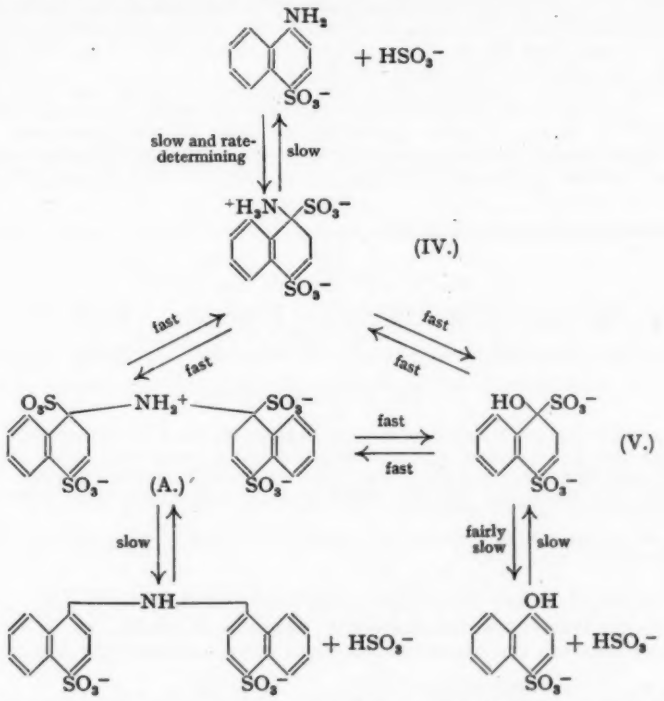
$+ NH_3$


(II.)


(III.)

Compound (III) is, of course, the simple analogue of substance (A) isolated from naphthionic acid, whilst (B) corresponds to either (I) or (II). The properties of (III) are actually similar to those of compound (A) in that they both evolve their nitrogen as ammonia and their sulphur as sulphite on alkaline hydrolysis.

Taken in conjunction with the kinetics outlined in Part I, the reaction between naphthionic acid and sodium bisulphite can be represented by the following detailed scheme :



It is interesting to note that this scheme accounts for the known occurrence of dinaphthylamine compounds as by-products (and even in some cases as main products) in the treatment of naphthylamines with sulphites or bisulphites (cf. Bucherer and Stohmann, *J. pr. Chem.*, 1905, **71**, 441; Bayer and Co., D.R.-P. 114,974).

Experimental.

Attempt to Prepare the Bisulphite Compound of 2-Naphthol-1-sulphonic Acid.—Crude sodium 2-naphthol-1-sulphonate was obtained from two different commercial sources (Messrs. B.D.H. and I.C.I. Dyestuffs Division) and purified by conversion into and recrystallisation of the aniline salt (cf. Forster and Keyworth, *J. Soc. Chem. Ind.*, 1927, **46**, 25T). Both samples of aniline salt had m. p. 178—179°, as compared with the recorded 182°. The purified aniline salt (27 g.) was converted into the monosodium salt by dissolving it in water (50 c.c.) and 2N-sodium hydroxide (90 c.c.), the aniline being extracted with ether. After being neutralised with concentrated hydrochloric acid and filtered through carbon, the sodium salt (15 g.) was salted out with A.R. sodium chloride (35 g.).

The monosodium salt (3 g.) was converted into disodium salt by dissolving it in boiling 90% alcohol (50 c.c.) and adding 50% aqueous sodium hydroxide (1 c.c.); it was filtered off and washed with cold alcohol (50 c.c.).

The disodium salt was dissolved in water (12 c.c.), and the solution saturated with sulphur dioxide. The solution, initially almost colourless, became bright yellow, but no solid separated even after several weeks' standing and repeated resaturation with the gas.

Re-examination of Woroshtzow's Preparation.—On repeating the preparation of disodium 2-naphthol-1-sulphonate outlined by Woroshtzow (*Ber.*, 1929, **62**, 61) and treating it with sulphur dioxide in aqueous solution, a crystalline solid separated in the way described. This reacted with iodine in neutral or alkaline solution and also formed sparingly soluble barium, copper, zinc, and mercury salts as claimed. However, conversion of the supposed disodium 2-naphthol-1-sulphonate into aniline salt gave needles, m. p. 262—263°, which is approximately that recorded by Forster and Keyworth (*loc. cit.*) for the aniline salt of 2-naphthol-6-sulphonic acid.

A purified sample of monosodium 2-naphthol-6-sulphonate was converted into disodium salt with 50% sodium hydroxide using alcohol, and on dissolving this in water and passing sulphur dioxide into the solution, the sparingly soluble monosodium salt separated in fine needles. Monosodium 2-naphthol-6-sulphonate reacts with iodine in neutral or alkaline solution, but not in acid medium; this would explain Woroshtzow's results on the supposed dissociation of the bisulphite compound. Finally, 2-naphthol-6-sulphonic acid forms sparingly soluble salts with the four metals mentioned above.

Isolation of Bisulphite Compounds from Naphthionic Acid.—Purified sodium naphthionate (130 g.) was dissolved in a warm solution of sodium bisulphite prepared by saturating sodium carbonate (212 g.) in water (800 c.c.) with sulphur dioxide. The solution was kept at 80° for 18 hours whilst a slow stream of sulphur dioxide was passed through it. At this stage no unchanged naphthionic acid was detected on acidification. The solution was cooled, made strongly acid to Congo-red with concentrated hydrochloric acid (300 c.c.), and a fast stream of nitrogen was passed through the solution, which was kept strongly acid, until all the sulphur dioxide was removed according to a test titration with iodine. Some inorganic salts were filtered off; the filtrate was evaporated to 250 c.c. under reduced pressure below 60°, and its pH was adjusted to 3·0 by addition of solid sodium hydrogen carbonate. Concentration and filtering from inorganic salts was continued until a thick syrupy residue remained, and this was stirred with about three times its volume of absolute alcohol. The mixture of bisulphite compounds slowly separated in two different types of large crystals, which were filtered off, air-dried, and separated from each other easily by hand picking.

The aggregates of needles (A) (approx. 85 g.) were recrystallised by dissolving them in water (85 c.c.) and adding absolute alcohol (260 c.c.) (Found: C, 32·82; H, 3·43; N, 2·12; S, 17·33; Na, 9·62. $C_{20}H_{16}O_{12}NS_4Na_3.4H_2O$ requires C, 32·82; H, 3·31; N, 1·91; S, 17·50; Na, 9·44%). On heating with aqueous sodium hydroxide, ammonia was evolved corresponding to 1·95% of N, and sulphite was formed which, on iodine titration, was equivalent to 8·50% of S.

The other type of crystal (B) (about 12 g.) (Found: C, 33·93; H, 4·20; S, 18·30; N, 3·49; Na, 6·40. $C_{10}H_{10}O_6NS_2Na,1\frac{1}{2}H_2O$ requires C, 33·89; H, 3·70; N, 3·95; S, 18·08; Na, 6·50%) with alkali yielded ammonia corresponding to 3·93% of N, and sulphite equivalent to 9·01% of S.

Conversion of Compound (A) into Compound (B).—The compound A (10 g.) was dissolved in water (10 c.c.), and a solution of ammonium iodide (10 g.) in absolute alcohol (20 c.c.) was added. On standing for 12 hours, compound B (5·0 g.) separated (Found: C, 33·12; H, 4·01; S, 18·73; Na, 6·60; N, available as ammonia, 3·64; S, available as sulphite, 8·94%). A further crop of the same material was obtained from the filtrate by adding more alcohol.

This experiment was repeated in presence of constant b. p. hydriodic acid (1 c.c.), and gave substantially the same results.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, March 30th,* 1946.]

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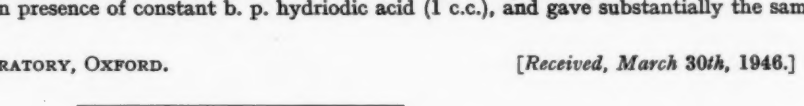
230. *The Mechanism of the Bucherer Reaction. Part III. Kinetics of the Reaction between Naphtholsulphonic Acids and Sodium Hydrogen Sulphite.*

By W. A. COWDREY.

The reaction between sodium 1-naphthol-4- and -5-sulphonates and sodium bisulphite has been studied kinetically. The process is reversible, the naphthol-bisulphite compound being formed by a bimolecular combination of naphthol and bisulphite and destroyed by a unimolecular dissociation. The rates and energies of activation of both the formation and the dissociation processes have been measured, together with the equilibrium constants.

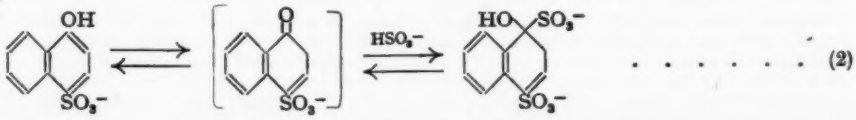
The mechanism of the reaction is discussed in relation to the earlier suggestion of Woroshtzow that naphthols ketonise before addition of bisulphite.

THE scheme outlined in Part II for the mechanism of the Bucherer reaction in the conversion of naphthylamines into naphthols involves six interconnected equilibria, only one of which can be studied in complete absence of the rest, namely, that between the naphthol-bisulphite compound and the free naphthol plus bisulphite:



. . . . . (1)

This type of reaction has been widely discussed in connection with the Bucherer reaction, and Woroshtzow (*J. Russ. Phys. Chem. Soc.*, **1915, 47, 1669**) suggested that the actual addition of bisulphite takes place to the keto-form of the naphthol:



. . . . . (2)

(cf. Adams, " Organic Reactions," Vol. I, p. 106).

This reaction has now been studied kinetically (in the light of the earlier observations of Parts I and II that bisulphite compounds of this type do not react with acid iodine) by measuring the rate at which the equilibrium is attained and also its composition. As in Part I, the kinetics were carried out in a large excess of sodium acetate–acetic acid buffer of pH 4·2 to avoid changes in pH which complicate analysis of the results.

Ignoring for the moment the possibility of the intermediate formation of the keto-form of the naphthol, and considering only the type of equilibrium of equation (1) above, then if a and b are the initial concentrations of naphthol and bisulphite, respectively, and x the concentration of bisulphite compound formed after a time t, the rate of disappearance of naphthol or bisulphite should be given by the expression

$$\frac{dx}{dt} = k_2(a - x)(b - x) - k_1x \quad . . . . . (3)$$

Here k_2 is the bimolecular velocity constant for the formation of the bisulphite compound and k_1 the unimolecular velocity constant for its dissociation. On integration this gives:

$$k_2 = \frac{1}{t(a + b + K - 2x_e)} \ln \frac{(a + b + K - x - x_e)x_e}{(a + b + K - x_e)(x_e - x)} \quad . . . . . (4)$$

where the equilibrium constant $K = k_1/k_2 =$ [Free naphthol] [HSO_3^-]/[Bisulphite compound] and x_e is the equilibrium concentration of bisulphite compound ($t = \infty$).

Kinetic measurements have been made with both 1-naphthol-4- and -5-sulphonic acids, and the results obtained could be quite satisfactorily interpreted on the basis of equation (4). The value of x_e was determined as the difference between the initial and the equilibrium bisulphite concentrations as measured by iodine titration, and from x_e the equilibrium constant could be calculated as $(a - x_e)(b - x_e)/x_e$. Then, by measuring

x, the fall in iodine titre over a time t, for a series of values of t, k_2 could be determined and hence k_1. Furthermore, by carrying out the reaction at a series of temperatures the energies of activation of both formation and dissociation processes were determined, and also the pre-exponential factor for the formation. The energies of activation were 16,800 and 20,800 cals./g.-mol. for the formation, and 24,200 and 25,600 cals./g.-mol. for the dissociation of the bisulphite compounds of 1-naphthol-4- and -5-sulphonic acids respectively, whilst the corresponding pre-exponential factors were 4·3 and 150 × 10^6 g.-mol.$^{-1}$ l. sec.$^{-1}$ (cf. Part I for the pre-exponential factors for the reaction of bisulphite with the corresponding amino-compounds).

The kinetic results are consistent with a simple equilibrium of the type represented by equation (1), it being assumed that the bisulphite adds directly to the C=C linkage in the manner suggested in Part I for the addition of bisulphite to naphthylamines. However, a mechanism involving the keto-form of the naphthol (equation 2) is also feasible provided that the equilibrium between keto- and enol forms of the naphthol is mobile (as it would be), the rate-determining step then being the addition of bisulphite ion to the keto-form. In this case the observed bimolecular constant k_2 will be a function of the equilibrium constant K_1 (= [Enol]/[Keto]) of the keto–enol equilibrium and the true bimolecular constant k_2', so that $k_2 = k_2'/(1 + K_1)$, whilst the observed energy of activation E is related to the true energy of activation of the reaction between the keto-form and bisulphite, E', by an expression which reduces to $E = E' + \Delta H$ if $K_1 \gg 1$ and ΔH is the heat absorbed in the conversion of enol to ketone.

It has not been possible to decide between these two possible types of mechanism by kinetic study.

Experimental.

Materials.—1-Naphthol-4- and -5-sulphonic acids were purified as their zinc salts by repeated recrystallisation from water (cf. Friedländer and Taussig, *Ber.*, 1897, **30**, 1459). The zinc salts were converted into sodium salts by addition of sodium carbonate, filtration from zinc carbonate, and salting out with sodium chloride from acid solution. They were dried at 90°, and analysis then showed them to be anhydrous.

Kinetic Measurements with 1-Naphthol-4-sulphonic Acid.—At 120·3°. Two solutions were prepared both 0·55M in acetic acid, 0·20M in sodium acetate, and 0·20M in sodium bisulphite, and containing sodium 1-naphthol-4-sulphonate (24·60 and 49·20 g. per 500 c.c.) corresponding to concentrations of 0·20M and 0·40M. These solutions were sealed up in 20-c.c. portions in glass tubes under nitrogen to prevent oxidation, and heated for known times at 120·3° before being cooled rapidly, diluted, and titrated by running into acidified iodine solution. The results were as follows, concentrations being expressed in g.-mol./l., and k_2 in g.-mol.$^{-1}$ l. hr.$^{-1}$:

t (hours).	[Bisulphite].	x.	10^2k_2.	t (hours).	[Bisulphite].	x.	10^2k_2.
(a) 0·20M-1-Naphthol-4-sulphonate.							
0·0	0·2025	—	—	18·0	0·1721	0·0304	7·2
3·0	0·1939	0·0086	7·9	40·5	0·1634	0·0391	6·1
7·5	0·1872	0·0153	6·2	69·5	0·1587	0·0438	—
11·0	0·1810	0·0215	6·7	150·0	0·1585	0·0440	—
						Average k_2 = 7·4 × 10^{-2}	

K = 0·56 g.-mol./l.; $k_1 = Kk_2$ = 0·042 hr.$^{-1}$.

0·40M-1-Naphthol-4-sulphonate.							
0·00	0·2000	—	—	15·00	0·1492	0·0508	7·37
3·00	0·1818	0·0182	7·55	20·00	0·1425	0·0575	7·18
5·00	0·1765	0·0235	7·16	26·00	0·1360	0·0640	7·41
6·75	0·1690	0·0310	7·57	35·00	0·1312	0·0688	7·35
9·50	0·1618	0·0382	7·22	45·00	0·1294	0·0706	—
12·00	0·1550	0·0450	7·41	77·50	0·1259	0·0741	—
						Average k_2 = 7·36 × 10^{-2}	

K = 0·555 g.-mol./l.; k_1 = 0·0408 hr.$^{-1}$.

The determinations at other temperatures were carried out with a solution corresponding to (b) above; at 100·2°, the values were k_2 = 2·26 × 10^{-2}, k_1 = 0·00640, K = 0·283, and at 80·0°, k_2 = 0·657 × 10^{-2}, k_1 = 0·00117, K = 0·179.

The plots of both log k_2 and log k_1 against $1/T$ are linear, and the slopes correspond to energies of activation of 16,800 and 24,200 cals./g.-mol., respectively.

Kinetic Measurements with 1-Naphthol-5-sulphonic Acid.—These measurements were carried out using the same concentrations and conditions as developed for 1-naphthol-4-sulphonic acid above, and k_2 is in the same units.

At 120·4°

t (hours).	[Bisulphite].	x.	10^2k_2.	t (hours).	[Bisulphite].	x.	10^2k_2.
0·0	0·2017	—	—	84·5	0·1598	0·0419	1·32
18·2	0·1844	0·0173	1·39	97·0	0·1568	0·0449	1·44
31·3	0·1802	0·0215	1·12	119·0	0·1558	0·0459	1·30
42·7	0·1711	0·0306	1·33	138·0	0·1540	0·0477	1·30
53·7	0·1701	0·0316	1·12	240·0	0·1520	0·0497	—
66·5	0·1617	0·0400	1·47			Average k_2 = 1·32 × 10^{-2}	

At 137·2°, the corresponding values were k_2 = 4·47 × 10^{-2}, k_1 = 0·0531, K = 1·19; and at 100·3°, k_2 = 0·360 × 10^{-2}, k_1 = 0·00244, K = 0·678.

Both log k_2 and log k_1 gave a linear plot against $1/T$, the slopes of which correspond to 20,800 and 25,600 cals./g.-mol. for the energies of activation.

The Physical Chemistry Laboratory, Oxford.

[*Received, March 30th*, 1946.]

231. *The Mechanism of the Bucherer Reaction. Part IV. The Kinetics of the Conversion of Naphthols into Naphthylamines.*

By W. A. Cowdrey.

The rate at which naphthols (1-naphthol-4- and -5-sulphonates) are converted into the corresponding naphthylamines by heating with ammonia and ammonium sulphite depends directly upon naphthol, ammonium- and sulphite-ion concentrations, and is independent of the excess concentration of free ammonia. The reaction is reversible, however, and the position of the equilibrium is dependent on free ammonia concentration and does not appear to be influenced by the presence of ammonium or sulphite ion.

These kinetic results have been interpreted as supporting the mechanism already put forward for the Bucherer reaction by Fuchs and Stix, with definite provisos regarding the relative velocities of the component reactions.

Various mechanisms have been proposed for the process discovered by Bucherer (*J. pr. Chem.*, 1904, **69**, 49) for preparing naphthylamines and *N*-substituted naphthylamines from the corresponding naphthols by heating with an aqueous solution of an amine and an amine sulphite; the one now most generally accepted is that put forward by Fuchs and Stix (see Part I). Although this probably outlines correctly most of the types of intermediate compound formed during the process, yet it gives little information about the factors which control either the positions of the various equilibria or the rates at which they are established. For example, four consecutive equilibria are postulated, involving four forward and four back reactions; nothing is known, however, of the relative speeds of the various reactions, nor is there any information as to which constitute the rate-determining steps in either direction. Such factors are of considerable interest and it was hoped that more precise knowledge of them would follow from a kinetic study of the process. The conversion of 1-naphthol-5-sulphonic acid (oxy-L acid) into 5-aminonaphthalene-1-sulphonic acid (Laurent acid) has therefore been studied kinetically at about 140°, the progress of the reaction being followed by the technique developed in Part I, *i.e.*, by determining the sparingly soluble aminonaphthalenesulphonic acid.

Experiments keeping the initial concentrations of the naphthol (0·10M) and ammonium sulphite (0·20M) fixed and varying only the initial concentration of free ammonia (from 0·20 to 0·40M) led to the surprising observation that the rate of formation of the naphthylamine was almost independent of the free ammonia concentration. Conversion into the amine was not complete, however, and it was evident that an equilibrium state was reached containing both naphthylamine and naphthol in amounts dependent on the ammonia concentration. Thus the higher the free ammonia concentration of the solution the higher was the concentration of naphthylamine formed at equilibrium, *i.e.*, the more efficient was the amination of the naphthol.

In a further set of measurements the concentrations of both sulphite and ammonium ions were separately varied at constant initial ammonia concentration. Here the results were very different; the rate of amination was now dependent on the concentration both of ammonium and of sulphite ions, the reaction being approximately of the first order with respect to each of these components. Thus by doubling the concentration of sulphite ions and keeping that of the ammonium ion constant (using a mixture of sodium and ammonium sulphites) or by doubling the ammonium-ion concentration without changing that of the sulphite (using a mixture of ammonium sulphite and sulphate) the rate of conversion of naphthol into naphthylamine was approximately doubled. The doubling of the concentration of ammonium sulphite, of course, resulted in a four-fold increase in the reaction velocity. The compositions at final equilibrium were, however, almost independent of the concentrations of either ammonium or sulphite ions.

Finally, variation of the initial concentration of the naphthol with ammonia, ammonium and sulphite ion constant showed that the reaction was approximately of the first order with respect to the naphthol. Thus the initial rate of conversion of naphthol (R·OH) into naphthylamine (R·NH_2) is given by the expression

$$d[R{\cdot}NH_2]/dt = -d[R{\cdot}OH]/dt = k_C[R{\cdot}OH][NH_4^+][SO_3^=] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Iodine titration showed that no significant change occurred in the free sulphite concentration throughout the reaction, indicating that no appreciable concentration of bisulphite compound is established at any stage. Thus in the conversion of naphthol into naphthylamine the net reaction can be represented by the equation

$$R{\cdot}OH + NH_3 \rightleftarrows R{\cdot}NH_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

which involves no change in the ammonium-ion concentration, and thus the rate expression (1) can be simplified to

$$d[R{\cdot}NH_2]/dt = k_C'[R{\cdot}OH] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $k_C' = k_C[NH_4^+][SO_3^=]$.

This expression takes no account of the back reaction, *i.e.*, the conversion of naphthylamine into naphthol. If the rate of the forward reaction is governed by the expression (3), and the complete equilibrium is represented by equation (2), the expression for the back reaction must be of the type:

$$\frac{d[R{\cdot}OH]}{dt} = \frac{-d[R{\cdot}NH_2]}{dt} = k_D'\frac{[R{\cdot}NH_2]}{[NH_3]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Combining (3) and (4) for the expression for the rate of attainment of equilibrium, we have

$$\frac{d[R{\cdot}NH_2]}{dt} = k_C'[R{\cdot}OH] - k_D'\frac{[R{\cdot}NH_2]}{[NH_3]}$$

where both k_C' and k_D' depend directly on $[NH_4^+]$ and $[SO_3^{=}]$. Then if the initial concentrations of naphthol and ammonia are a and b respectively, and the concentration of naphthylamine increases from zero to x in a time t,

$$dx/dt = k_C'(a - x) - k_D'x/(b - x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The integration of this expression as it stands is too cumbersome to be of simple application. By making the rough approximation, however, that the relative fall in ammonia concentration is small over the reaction, *i.e.*, that $(b - x)$ is not greatly different from b for all values of x, then the expression simplifies to

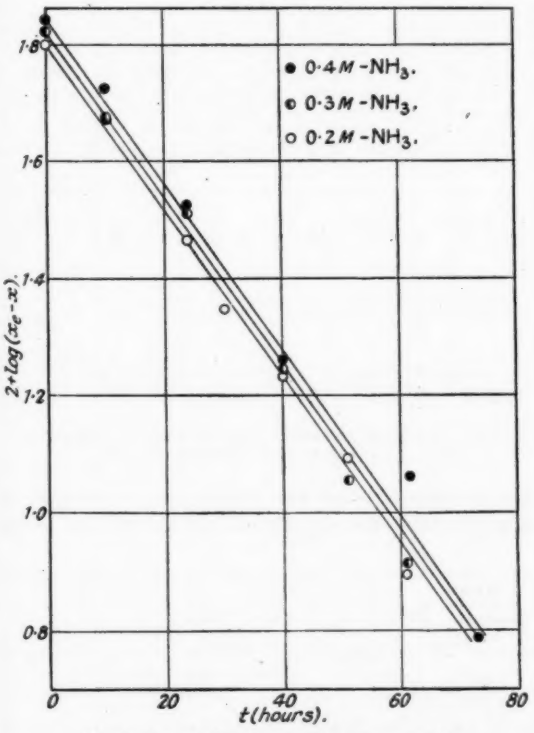
$$dx/dt = k_C'(a - x) - k_D'x/b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

which on integration gives for the first-order velocity constant of the forward reaction :

$$k_C' = k_C[NH_4^+][SO_3^{=}] = \frac{x_e}{at} \ln \frac{x_e}{(x_e - x)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

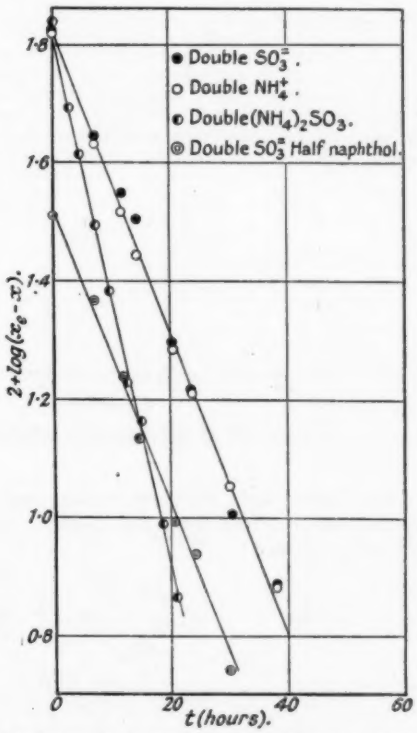
where x_e is the equilibrium naphthylamine concentration.

FIG. 1.



Variation of free ammonia concentration.

FIG. 2.



Variation in initial concentrations of naphthol, sulphite, and ammonium ion.

If equation (7) is applicable, a test plot of log $(x_e - x)$ against t should give a straight line of slope $\frac{-k_C[NH_4^+][SO_3^{=}]a}{2{\cdot}303\ x_e}$ and an intercept of log x_e. Fig. 1 illustrates such a test plot for the series of experiments in which only the initial free ammonia concentration was varied, whilst Fig. 2 shows the effect of separate variations in $[NH_4^+]$, $[SO_3^{=}]$, and [R·OH] at a constant initial ammonia concentration. Both sets of results satisfactorily confirm the applicability of the rate equation (7).

The equilibrium constant of the reaction given in equation (2) can be calculated from the equilibrium concentration x_e as

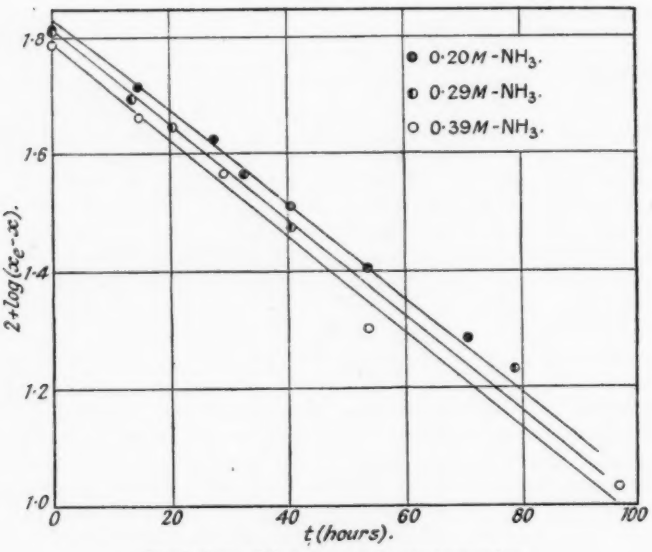
$$K = \frac{[R{\cdot}NH_2]}{[R{\cdot}OH][NH_3]} = \frac{x_e}{(a - x_e)(b - x_e)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Calculations of K for various initial concentrations of naphthol, ammonia, ammonium and sulphite ion are given in Table I; in view of the fact that the measurements are not of high accuracy because they all refer to equilibria established well over towards naphthylamine formation, the agreement is quite reasonable.

In a similar investigation of the conversion of 1-naphthol-4-sulphonic acid into naphthionic acid the kinetics were of the same general form, but the reaction was of significantly less than the first order with respect to both sulphite ion and naphthol (see Figs. 3 and 4). The rate of conversion of the 1 : 4- was slower than that

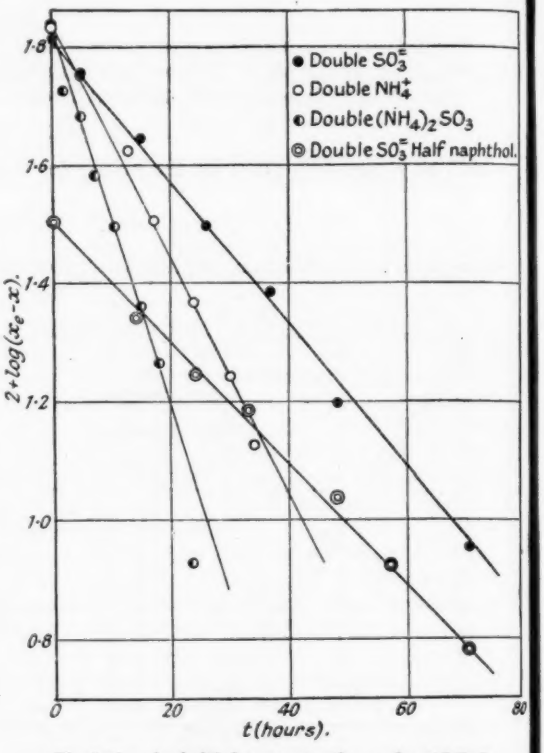
of the 1 : 5-acid, in contrast with the reverse type of reaction discussed in Part I where the 1 : 4-compound reacted more rapidly.

FIG. 3.



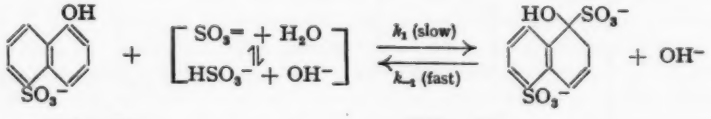
Variation of free ammonia concentration.

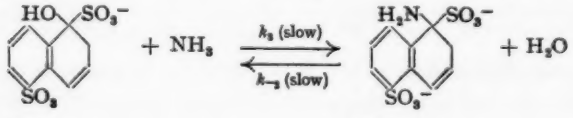
FIG. 4.

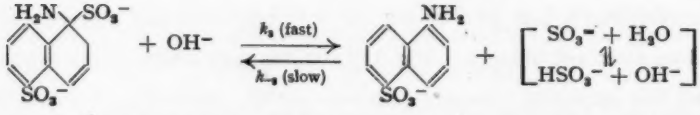


Variation in initial concentrations of naphthol, sulphite, and ammonium ion.

The systematic kinetics which have been observed are consistent with the Fuchs and Stix type of mechanism provided that the relative velocities of the various reactions are approximately as outlined in the following scheme:

(i) 

(ii) 

(iii) 

Analysis of this reaction system by the method of Christiansen's formulation (*Z. physikal. Chem.*, **1936**, **33**, *B*, 145; **1937**, **37**, *B*, 374) gives for the reciprocal velocities in either direction,

$$\frac{dt}{d[R{\cdot}NH_2]} = \frac{1}{k_1[R{\cdot}OH][SO_3^=]}\left\{1 + \frac{k_{-1}[OH^-]}{k_2[NH_3]} + \frac{k_{-1}k_{-2}}{k_2k_3[NH_3]}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

and

$$\frac{dt}{d[R{\cdot}OH]} = \frac{1}{k_3[R{\cdot}NH_2][SO_3^=]}\left\{1 + \frac{k_2[OH^-]}{k_{-2}} + \frac{k_2k_3[NH_3]}{k_{-2}k_{-1}}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

These two expressions correspond to the observed kinetics provided that $k_{-1} \gg k_2$ and $k_3 \gg k_{-2}$, when

$$\frac{d[R{\cdot}NH_2]}{dt} = \frac{k_2k_1}{k_{-1}K_B}[R{\cdot}OH][SO_3^=][NH_4^+] - \frac{k_{-2}k_{-3}}{k_3K_B}[R{\cdot}NH_2][SO_3^=][NH_4^+] \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where K_B is the basic dissociation constant of ammonia. This is of the same form as equation (4). The values of k_1 and k_{-2} must be considerably less than k_{-1} and k_2 to satisfy the condition that appreciable concentrations of bisulphite compounds are not set up at any stage.

No account has been taken in this analysis of the idea that the naphthol reacts in its keto-form as suggested by Woroshtzow. As in Part III, however, there is no need to postulate ketonisation before formation of bisulphite compound to account for the observed kinetics, but if it does occur then the keto-enol equilibrium must be mobile.

The simultaneous formation of the dinaphthylamine derivative has also been ignored, although it is very probable that it occurs to some extent. Any treatment taking account of this side reaction would be considerably more complicated, and in any case the absence of a satisfactory method of estimating the dinaphthylamine compound necessitates this omission.

Experimental.

Solutions were prepared having known concentrations of ammonium ion, sulphite ion, and free ammonia (estimated by iodine titration and Kjeldahl analysis) and containing the requisite concentration of the sodium naphtholsulphonate (by direct weighing). The total ionic strength was kept constant by adding sodium sulphate. Portions of the solutions (40 c.c.) were sealed under nitrogen in soft-glass tubes, preheated for 5 minutes in a bath at 100°, and then heated for known times in oil cups surrounded by a xylene-vapour bath at 139°. Reaction was arrested by dropping the tubes into a large bath of cold oil, and the contents of the tubes were acidified with concentrated hydrochloric acid (4 c.c.). The naphthylaminesulphonic acid thus precipitated was slightly contaminated with silica as a result of attack on the glass tube by the alkali. After the acid had been collected by filtration in a sintered-glass crucible and dried, the crucible was washed out with dilute ammonia to give the true weight of naphthylaminesulphonic acid x (g. per 40 c.c.) formed in a time t (hours) by difference. The equilibrium concentration x_e corresponds to the usual "infinity" measurement.

Amination of Sodium 1-Naphthol-5-sulphonate.—(1) Variations in initial ammonia concentration with fixed initial concentrations of $SO_3^=$ (0·200M), NH_4^+ (0·400M), sodium 1-naphthol-5-sulphonate (0·100M), and sodium sulphate (0·200M).

0·20M-NH_3.

t	10·0	24·0	30·0	40·0	51·0	61·0	∞
x	0·1537	0·3400	0·4075	0·4592	0·5058	0·5507	0·6300

0·30M-NH_3.

t	10·0	24·0	40·0	51·0	61·0	∞
x	0·1918	0·3446	0·4960	0·5560	0·5876	0·6700

0·40M-NH_3.

t	10·0	24·0	40·0	61·5	73·0	∞
x	0·1742	0·3710	0·5267	0·5895	0·6434	0·7050

(2) Variations in initial concentrations of ammonium ion, sulphite ion, and sodium 1-naphthol-5-sulphonate with fixed initial concentrations of free ammonia (0·30M).

0·200M-$(NH_4)_2SO_3$; 0·200M-Na_2SO_3; 0·100M-Na 1-naphthol-5-sulphonate.

t	7·50	12·0	14·5	20·5	24·0	30·0	38·0	∞
x	0·2340	0·3347	0·3857	0·4710	0·5010	0·5505	0·5870	0·6630

0·200M-$(NH_4)_2SO_3$; 0·200M-$(NH_4)_2SO_4$; 0·100M-Na 1-naphthol-5-sulphonate.

t	7·50	12·0	14·5	20·5	24·0	30·0	38·0	∞
x	0·2320	0·3197	0·3533	0·4749	0·5096	0·5720	0·5958	0·6730

0·200M-$(NH_4)_2SO_3$; 0·200M-Na_2SO_3; 0·050M-Na 1-naphthol-5-sulphonate.

t	7·50	12·0	14·8	20·5	24·0	30·0	38·0	∞
x	0·0900	0·1510	0·1860	0·2250	0·2370	0·2683	0·2892	0·3232

0·400M-$(NH_4)_2SO_3$; 0·100M-Na 1-naphthol-5-sulphonate.

t	3·50	5·00	7·50	10·0	13·0	15·0	18·5	21·0	24·0	∞
x	0·1880	0·2715	0·3760	0·4440	0·5170	0·5390	0·5875	0·6110	0·6285	0·6850

(3) Calculations of the equilibrium constant K (concentrations expressed as g.-mol. per l.).

Table I.

Initial [NH_3].	Initial [Naphthol].	[NH_4^+].	[$SO_3^=$].	Equilibrium [Naphthylamine].	K.
0·20	0·10	0·40	0·20	0·071	19
0·30	0·10	0·40	0·20	0·075	13
0·40	0·10	0·40	0·20	0·079	12
0·30	0·10	0·40	0·40	0·074	13
0·30	0·10	0·80	0·20	0·075	13
0·30	0·05	0·40	0·40	0·036	10
0·30	0·10	0·80	0·40	0·077	15

Amination of Sodium 1-Naphthol-4-sulphonate.—(1) Variations in initial ammonia concentration with fixed initial concentrations of $SO_3^=$ (0·195M), NH_4^+ (0·390M), sodium naphthionate (0·100M), and sodium sulphate (0·200M).

0·20M-NH_3.

t	15·0	29·5	54·0	96·5	∞
x	0·1543	0·2445	0·4148	0·5075	0·6140

0·29M-NH_3.

t	14·0	21·0	33·0	41·0	79·0	∞
x	0·1461	0·2100	0·2830	0·3530	0·4800	0·6500

0·39M-NH_3.

t	15·0	28·0	41·0	54·0	71·0	∞
x	0·1388	0·2378	0·3367	0·4080	0·4685	0·6603

(2) Variations in initial concentrations of ammonium ion, sulphite ion, and sodium naphthionate with fixed initial concentrations of free ammonia (0·29M).

0·195M-$(NH_4)_2SO_3$; 0·202M-Na_2SO_3; 0·100M-sodium naphthionate.

t	5·0	15·0	26·0	36·7	48·0	70·0	∞
x	0·0852	0·2113	0·3385	0·4100	0·4950	0·5610	0·6500

0·195M-$(NH_4)_2SO_3$; 0·195M-$(NH_4)_2SO_4$; 0·100M-sodium naphthionate.

t	5·0	13·0	17·2	24·0	30·0	34·2	48·0	71·0	∞
x	0·1260	0·2695	0·3672	0·4550	0·5120	0·5530	0·5970	0·6395	0·6850

0·195M-$(NH_4)_2SO_3$; 0·200M-Na_2SO_3; 0·050M-sodium naphthionate.

t	14·0	24·0	33·0	48·0	57·0	70·0	∞
x	0·0998	0·1435	0·1672	0·2110	0·2365	0·2600	0·3205

0·392M-$(NH_4)_2SO_3$; 0·100M-sodium naphthionate.

t	2·0	5·0	7·25	10·5	15·0	18·0	23·5	41·2	∞
x	0·0840	0·2127	0·3118	0·3800	0·4624	0·5078	0·6060	0·6690	0·6900

(3) Calculations of the equilibrium constant.

TABLE II.

Initial $[NH_3]$.	Initial [Naphthol].	$[NH_4^+]$.	$[SO_3^=]$.	Equilibrium [Naphthylamine].	*K*.
0·20	0·10	0·39	0·20	0·069	17
0·30	0·10	0·39	0·20	0·073	21
0·40	0·10	0·39	0·20	0·075	24
0·30	0·10	0·39	0·40	0·073	21
0·30	0·10	0·78	0·20	0·077	27
0·30	0·05	0·39	0·40	0·036	10
0·30	0·10	0·78	0·39	0·077	27

The author is grateful to Professor C. N. Hinshelwood for valuable help and advice throughout this work.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, March 30th*, 1946.]

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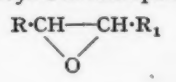
232. *Reactions of Ethylene Oxides. Part I. Preparation of Ethylene Sulphides and Trithiocarbonates.*

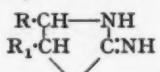
By C. C. J. CULVENOR, W. DAVIES, and K. H. PAUSACKER.

Some simple ethylene oxides are converted into the corresponding ethylene sulphides by the action of thiourea, thiocyanates, and thiocarbanilide. Control of the experimental conditions diminishes the amount of high-molecular material sometimes formed, which, however, is the exclusive product from glycidol and styrene oxide. The characteristic sparingly soluble yellow trithiocarbonates are obtained from some simple ethylene oxides and sulphides by the action of xanthates. *cyclo*Hexene oxide with sodium trithiocarbonate, and cyclo*hexene sulphide* with this and higher thiocarbonates, Na_2CS_n (n = 3—6), yield cyclo*hexene trithiocarbonate*, whereas this product, mixed with a white compound, m. p. 155·5°, is obtained from *cyclo*hexene oxide and the perthiocarbonates.

BODFORSS (*Ber.*, 1918, **51**, 212) showed that 1-benzoyl-2-*m*-nitrophenylethylene oxide (I; R = Bz, R_1 = *m*-$C_6H_4{\cdot}NO_2$) reacted with thiourea to form 2-imino-4-benzoyl-5-*m*-nitrophenylthiazolidine (II) or the isomeric 2-imino-5-benzoyl-4-*m*-nitrophenylthiazolidine (III); thiocarbanilide behaved similarly. Olin and Dains (*J. Amer. Chem. Soc.*, 1930, **52**, 3322) found that ethylene oxide and thiocarbanilide gave *NN'*-diphenyl-2-hydroxyethyl*iso*thiourea, $CH_2(OH){\cdot}CH_2{\cdot}S{\cdot}C(NPh){:}NHPh$, and thiourea apparently gave the unstable 2-hydroxyethylthiourea. On the other hand, it was claimed by Dachlauer and Jackel (D.R.-P. 636,708) that ethylene oxide and thiourea or potassium thiocyanate gave good yields of ethylene sulphide, and that glycidol, epichlorohydrin, and propylene oxide behaved similarly. The few aliphatic ethylene sulphides described in the literature had usually been prepared by the action of sodium sulphide on 1 : 2-dithiocyanates or halogenothiocyanates (Delépine and Jaffeux, *Compt. rend.*, 1921, **172**, 158).



(I.)



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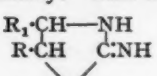


(III.)

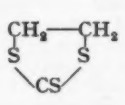
The present work shows that the course of the reaction with thiourea partly depends on the structure of the ethylene oxide used. The ethyl ester of dimethylglycidic acid and benzylideneacetone oxide yield derivatives

containing both nitrogen and sulphur. Simpler oxido-compounds behave differently, and the monomeric sulphides of ethylene, propylene, chloropropylene, *iso*butylene and *cyclo*hexene are obtained in good yield from the corresponding oxides. The use of *cyclo*hexene oxide in a series of comparative experiments shows that ammonium or potassium thiocyanate tends to cause polymerisation and to give lower yields of the monomeric sulphide than does thiourea. With thiocarbanilide, the reaction is very sluggish. It should be noted that, despite the above patent, the monomeric sulphide from glycidol has not been obtained from any of the above reagents, and the b. p. of *3-chloropropylene sulphide* is 79—81°/114 mm. or 138—139°/760 mm., and not 94—96°/6 mm. It is evident that the use of the reagents requires careful control; *e.g.*, Engle (*J. Amer. Chem. Soc.*, 1898, **20**, 676) claims that the only substance isolated in the reaction between epichlorohydrin and potassium thiocyanate is epithiocyanohydrin.

Potassium selenocyanate and *cyclo*hexene oxide yield *cyclo*hexene and selenium, and not *cyclo*hexene selenide.

The action of at least 2 mols. of metallic xanthates on ethylene oxide gives a 97% yield of ethylene trithiocarbonate (IV), which is also produced by the same reagent with ethylene chlorohydrin and with ethylenedithiol. Similarly, cyclo*hexene trithiocarbonate* (VI) is formed from *cyclo*hexene oxide, 2-chloro*cyclo*hexanol, and cyclo*hexene sulphide*, and *tetramethylethylene trithiocarbonate* (in small yield) is likewise formed from the oxide. Experiments so far show that there always is a reaction between xanthate and a compound with an undoubted ethylene oxide structure, but in some cases, *e.g.*, epichlorohydrin and glycidol, the products are polymeric.

Variation of the amounts of potassium hydroxide reacting with methyl-alcoholic solutions of *cyclo*hexene oxide and sulphide containing excess of carbon disulphide indicates that the oxide is first converted by the xanthate into the sulphide, which then very rapidly reacts with more xanthate to form the intermediate (V), which loses potassium methoxide (available for further xanthate formation) to form (VI). The use of 0·1 mol. of potassium hydroxide with the sulphide gives a yield of over 80% of (VI), which is also slowly formed through the agency of the alkali in the glass of the vessel in which the operation is carried out. It is noteworthy that, whilst all attempts to make styrene sulphide give merely high-molecular material, styrene oxide with xanthate gives *styrene trithiocarbonate* in 77% yield.



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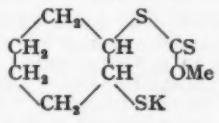

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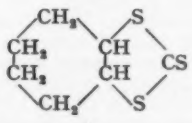

(VI.)

The action of the salts of thiocarbonic acids on ethylene oxides has been chiefly carried out with *cyclo*hexene oxide, though in this case polymers are sometimes formed. *cyclo*Hexene oxide and Na_2CS_3 give (VI) in 39% yield, whereas Na_2CS_4, Na_2CS_5, and Na_2CS_6 produce a mixture of (VI) and colourless crystals. The above four salts and *cyclo*hexene sulphide give (VI) alone.

These colourless crystals crystallise well from benzene and melt at 155·5°. Upon standing in the air the m. p. may fall to 132° although it is unaltered if the substance is kept in a vacuum desiccator over phosphoric oxide. Both sublimation in a high vacuum and heating in a water-oven raise the m. p. of the low-melting forms. This apparent hydrate formation is being further investigated.

Experimental.

Preparation of Ethylene Sulphides.—The reaction between ethylene oxides and some of the thio-reagents can be very vigorous, and the low temperatures mentioned can usually be maintained only by efficient external cooling. Some aliphatic sulphides are unstable in the presence of acid or alkali solutions, and any sudden rise of temperature during the reaction results in formation of little monomeric sulphide and much insoluble non-volatile material. The table indicates variations in yields of ethylene sulphides with various reagents and conditions. As the reaction proceeds, the pH of the

Oxide.	Reagent.	Conditions.	Yield, %.	Residue, %.
*cyclo*Hexene oxide (5 g.)	Thiourea (5 g.)	32 hrs. at 15°	40	—
		1·5 hrs. at 60°	58	15·5
		3 hrs. at 60°	55	24
	KCNS (7·5 g.)	24 hrs. at 15°	43·5	—
		1 hr. at 60°	61	—
		2 hrs. at 60°	42	—
		3 hrs. at 60°	—	100
	NH_4CNS (7 g.)	1·5 hrs. at 60°	60	—
		3 hrs. at 60°	43	55
Epichlorohydrin (11·6 g.) *		1 hr. at 0° and then at 20° for		
	Thiourea (10·5 g.)	3 hrs.	67	—
	KCNS (15 g.)	6 hrs.	47	16
	NH_4CNS (15 g.)	3 hrs.	38	30
*iso*Butylene oxide (5 g.) †		Time (hrs.) at 20°		
	Thiourea (6 g.)	3·25	39	—
		17·5	57	—
		30	51	13

* In 35 ml. of methyl alcohol. When water is used instead of methyl alcohol, lower yields are obtained.

† Very small yields of sulphide obtained when water is used instead of methyl alcohol. This sulphide is extracted with ether.

medium and the yield of polymeric residual compound usually increase. The following details of the process for the formation of cyclo*hexene sulphide* apply essentially to the other reactions in the table. *cyclo*Hexene oxide (5 g.) and methyl alcohol (20 ml.) are treated with the reagent shown in the table, the product poured into water (150 ml.) and the mixture extracted with chloroform. *cyclo*Hexene sulphide has b. p. 67—68°/16 mm., $n_D^{20°}$ 1·5309 (Found: S, 28·0. $C_6H_{10}S$ requires S, 28·05%). Refluxing *cyclo*hexene oxide (6 g.) and thiocarbanilide (11·7 g.) in ethyl alcohol (25 ml.) gives in 2 hours a 15%, and in 13 hours a 37%, yield of the sulphide. The sulphides described have slightly unpleasant odours.

3-Chloropropylene sulphide has b. p. 79—81°/114 mm., 138—139°/760 mm., $n_D^{20°}$ 1·5280 (Found: S, 29·8; Cl, 32·9. C_3H_5ClS requires S, 29·5; Cl, 32·7%). It is slowly decomposed by cold brine, forming a white insoluble solid. *iso-Butylene sulphide* has b. p. 87°/760 mm., $n_D^{17°}$ 1·4661 (Found: S, 36·7. C_4H_8S requires S, 36·4%).

Propylene sulphide is obtained in 61% yield when propylene oxide (5 g.), thiourea (7 g.), ice (10 g.), and water (15 ml.) are stirred at 0° for 0·5 hour, and at 20° for a further 3 hours; it has b. p. 75—76°, $n_D^{18°}$ 1·4780. Delépine and Jaffeux (*loc. cit.*) record b. p. 75—77°, $n_D^{19°}$ 1·473.

cyclo*Hexene Trithiocarbonate* (VI).—*cyclo*Hexene oxide reacts immediately in the cold with alkali xanthates in alcohol but is unaffected by carbon disulphide alone over a period of two months. A solution of potassium hydroxide (3·50 g., 2½ mols.) in methyl alcohol (15 ml.) containing carbon disulphide (5·7 g., 3 mols.) is treated at room temperature with *cyclo*hexene oxide (2·45 g., 1 mol.), the mixture kept overnight, water (100 ml.) added, and the product heated on the water-bath until carbon disulphide is removed. cyclo*Hexene trithiocarbonate* (thick yellow crystals, 87% yield), moderately soluble in cold benzene, sparingly soluble in cold alcohol, has m. p. 169° (Found: S, 50·1. $C_7H_{10}S_3$ requires S, 50·5%). Lower yields are given by less than 2 mols. of carbon disulphide with alcoholic alkali. Similarly, a 95% yield of the trithiocarbonate is rapidly obtained from *cyclo*hexene sulphide, and a 43% yield from 2-chloro*cyclo*hexanol. Lower yields are obtained when water is used instead of methyl alcohol.

Ethylene Trithiocarbonate.—Ethylene oxide (2·2 g., 1 mol.), with carbon disulphide (11·4 g., 3 mols.), potassium hydroxide (7·0 g., 2½ mols.), and methyl alcohol (25 ml.), requires efficient cooling to prevent loss and gives a 97% yield of ethylene trithiocarbonate, yellow crystals from benzene–light petroleum, m. p. 36—37° (Found: S, 71·0. Calc. for $C_4H_4S_3$: S, 70·6%); it was identified by mixed m. p. with the compound obtained (78% yield) after Husemann (*Annalen*, 1862, **123**, 83) by the action of ethylene dibromide on sodium trithiocarbonate. Ethylene trithiocarbonate is obtained in 83% yield by allowing ethylenedithiol (2·0 g.) to stand for 5 days with methyl alcohol (15 ml.) containing carbon disulphide (2·5 g.) and potassium hydroxide (1·5 g.), or in 42% yield by allowing ethylene chlorohydrin (2·0 g.) to stand for 3 days with methyl alcohol (15 ml.) containing carbon disulphide (5·7 g.) and potassium hydroxide (3·15 g.).

Styrene Trithiocarbonate.—Styrene trithiocarbonate is obtained in 77% yield when styrene oxide (2 g., 1 mol.), potassium hydroxide (2·2 g., 2·25 mols.), and carbon disulphide (3·2 g., 2·5 mols.) in methyl alcohol react at room temperature for 24 hours; yellow needles, m. p. 87—88°, very soluble in benzene, much less soluble in alcohol (Found: S, 45·2. $C_9H_8S_3$ requires S, 45·3%).

Tetramethylethylene Trithiocarbonate.—Tetramethylethylene oxide (2 g.), carbon disulphide (3·8 g.), potassium hydroxide (2·6 g.), and methyl alcohol (15 ml.), after three weeks at 36° and then addition of water, give the *trithiocarbonate* as yellow crystals from alcohol (yield 0·2 g.), m. p. 156° (Found: S, 49·8. $C_7H_{12}S_3$ requires S, 50·0%).

Action of Sodium Thiocarbonates on cyclo*Hexene Oxide and Sulphide.*—The alcoholic solution of sodium trithiocarbonate is made by admixture of the hydrated sulphide and carbon disulphide with alcohol. Fresh solutions of the perthiocarbonates, using appropriate proportions of sulphur, are made and used as exemplified in the following account of the action of Na_2CS_4 on *cyclo*hexene oxide. Water (9 ml.), sulphur (1 g., 1½ mols.), and sodium sulphide nonahydrate (7·5 g., 1½ mols.) are heated until the sulphur dissolves, then cooled, methyl alcohol (35 ml.) and carbon disulphide (2·9 g., 1½ mols.) added, and shaking is continued until the last dissolves. *cyclo*Hexene oxide (2·45 g., 1 mol.) is then added, and the mixture kept at room temperature for 3 weeks. It is then treated with water (200 ml.), and cooled; the light yellow precipitate (2·6 g.) is collected and crystallised from benzene, and the more soluble *cyclo*hexene trithiocarbonate separated from the less soluble colourless crystals (1·1 g.), m. p. 154·5—155·5°. Na_2CS_5 and Na_2CS_6 give a similar mixture. *cyclo*Hexene oxide with 1½ and 2½ mols. of the trithiocarbonate give a 39% yield of *cyclo*hexene trithiocarbonate, which compound is also formed from *cyclo*hexene sulphide and Na_2CS_3, Na_2CS_4, Na_2CS_5, and Na_2CS_6.

ORGANIC CHEMICAL LABORATORY, UNIVERSITY OF MELBOURNE. [*Received, March 12th*, 1946.]

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233. *A New Synthesis with Maleic Anhydride.*

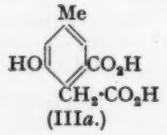
By ENDRE BERNER.

An addition was found to take place even at ordinary temperature between one mol. of acetylacetone and two mols. of maleic anhydride. It is suggested that the maleic anhydride first formed double molecules by a substitution addition, and that in a second stage the acetylacetone was added to the double molecules. By treatment with concentrated sulphuric acid the adduct lost water, giving a derivative of *iso*coumaranone which could be degraded to *p*-xylenol. The adduct and the dehydrated product showed, when treated with weak alkali, an interesting colour phenomenon caused by enolising processes. Maleic anhydride was found to react in a similar way with ethyl acetoacetate.

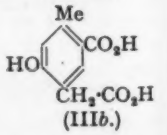
A β-DIKETONE is generally more or less enolised, and in some cases there is evidence of the existence even of dienols which would contain two accumulated double bonds. In the case of the simplest β-diketone, acetylacetone (I), it may be assumed that a dienol (II) could also exist. Such a dienol ought to react with maleic

$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$ (I.)

$CH_3{\cdot}C(OH){:}CH{\cdot}C(OH){:}CH_2$ (II.)



(III*a*.)



(III*b*.)

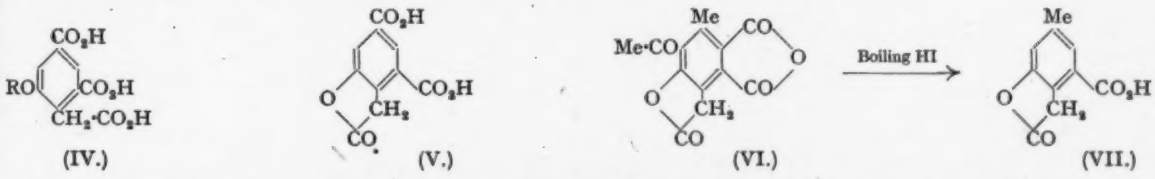
anhydride or other dienophilic compounds. In order to test this assumption, a mixture of acetylacetone and maleic anhydride was heated at 110—115° for two hours. It was apparent that a reaction had taken place for, on being kept for some time, the mixture deposited crystals of a new compound. It was found later that the

reaction took place even at room temperature, though very slowly, and for practical purposes a temperature of 70—80° was found the most suitable.

Assuming the reaction to be an addition of one mol. of maleic anhydride to one mol. of acetylacetone, a compound $C_9H_{10}O_5$ should have been formed. Analysis of the new compound showed, however, the remarkable result that addition had taken place between one mol. of acetylacetone and two mols. of maleic anhydride, the *adduct* having the molecular formula $C_{13}H_{12}O_8$ (VIII). The adduct was both a lactone and an acid anhydride, and it readily combined with one mol. of water, giving a crystalline *substance*, $C_{13}H_{14}O_9$. For total neutralisation the adduct required 3 equivs. of alkali. A solution of the adduct in ethyl acetate did not add on bromine. In a freshly prepared aqueous solution, however, addition of bromine took place. This solution also gave a red-violet colour with ferric chloride. By catalytic hydrogenation four atoms of hydrogen were taken up. The adduct was easily oxidised by potassium permanganate.

Before discussing the constitution of the adduct (VIII) and the manner of its formation, it is necessary to consider some of the degradation products. By treatment of the adduct with concentrated sulphuric acid two mols. of water were split off, an aromatic compound $C_{13}H_8O_6$ (VI) being obtained. This was both an acid anhydride and a lactone. As will be shown it can, however, be regarded as a derivative of coumaran or, better, of *iso*coumaranone.

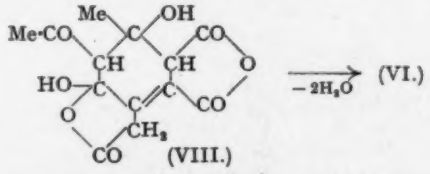
When the dehydrated adduct (VI) was boiled for some hours with concentrated hydriodic acid in the presence of red phosphorus no reduction took place, but one mol. of acetic acid and one mol. of carbon dioxide were split off, a colourless, crystalline substance $C_{10}H_8O_4$ (VII) being formed. This substance was also a lactone and contained one free carboxyl group. The corresponding hydroxy-dicarboxylic *acid*, $C_{10}H_{10}O_5$, was obtained by acidifying the alkaline solution. It gave by methylation with methyl sulphate a compound containing three methoxyl groups, two of which could be removed by hydrolysis. The total decarboxylation of the acid, achieved by heating the sodium or calcium salt with calcium hydroxide, led to *p*-xylenol. The acid may therefore be either 5-*hydroxy*-3-*carboxy*-p-*tolueneacetic acid* (III*a*) or the 2-carboxy-isomer (III*b*); no other structure is possible, because the parent substance (VI) is an acid anhydride and therefore must be derived from an acid having two adjacent carboxyl groups. In order to decide between (III*a*) and (III*b*) the following reactions were carried out. By oxidation of the *methyl ether* of (III*a*) with potassium permanganate the nuclear methyl group was converted into a carboxyl group, and a methoxy-tricarboxylic *acid* (IV, R = Me) was formed. When the corresponding hydroxy-tricarboxylic acid (IV, R = H), obtained by treatment with hydriodic acid, was sublimed in a high vacuum it lost only one mol. of water, yielding the lactonic iso*coumaranone*-4 : 6-*dicarboxylic acid*, $C_{10}H_6O_6$ (V). From this it is evident that the compound $C_{10}H_{10}O_5$ must have the formula (III*a*); for if formula (III*b*) had been correct, two molecules of water should have been lost during the sublimation, giving $C_{10}H_4O_5$, which would also have contained an acid anhydridic ring.



(IV.) (V.) (VI.) (VII.)

The compound $C_{10}H_8O_4$, obtained by the action of hydriodic acid on the dehydrated adduct, must be 6-*methyl*iso*coumaranone*-4-*carboxylic acid* (VII), and accordingly the dehydrated adduct must be the *anhydride* of 7-*acetyl*-6-*methyl*iso*coumaranone*-4 : 5-*dicarboxylic acid* (VI). The formation of acetic acid during the boiling with hydriodic acid was remarkable, because the acetyl group is attached directly to the benzene nucleus. It must, however, have been due to the fact that the nucleus was fully substituted. There can be no doubt that (VI) was a methyl ketone, for it gave iodoform on treatment with an alkaline solution of iodine.

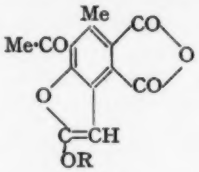
The adduct itself is formulated as (VIII) on the basis of its relationship to (VI) and the fact that it is formed from 1 mol. of acetylacetone and 2 mols. of maleic anhydride. The formula (VIII) does not show hydrogen bonds which undoubtedly exist between each of the two hydroxyl groups and the nearest carbonyl group.



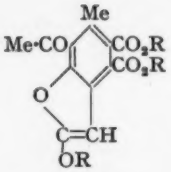
(VIII.)

The anhydride (VI) dissolved rapidly in aqueous sodium carbonate giving a blood-red solution which in a few minutes turned yellow. With sodium hydroxide the same dark red colour appeared, but in this case it turned yellow immediately. It is suggested that the action of the alkali in the first instance results in an enolisation only at the group ·CH_2·CO·, giving a soluble enolate (IX, R = Na) the colour of which is ascribed to the 7 double bonds, all of which take part in a crossed conjugated system. The intensity of the colour of the primarily-formed enolate must be due to the fact that two of the carbonyl groups in the conjugated system form

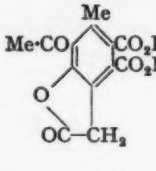
part of a heterocyclic ring for, when this ring was opened by the continued action of alkali, the colour brightened and became yellow (X, R = Na).



(IX.)
(R = Na, red; R = Me, yellow.)



(X.)
(R = Na, yellow; R = H, yellow; R = Me, almost colourless.)

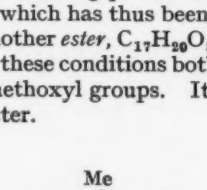


(X*a*.)
(Colourless.)

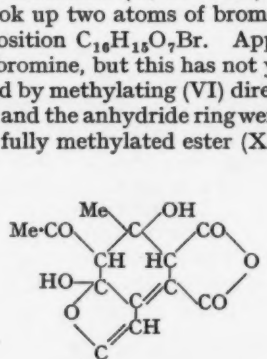
The red enolate still contained the acid anhydride ring, for, if the red solution was acidified, a colourless substance separated which was identical with the original dehydrated compound. If, however, the solution was acidified only after it had become yellow, the colour of the solution turned lighter yellow, but no precipitation took place. When this solution was left for some time excellent crystals of a bright yellow substance were formed. This *substance* (X, R = H) had m. p. 160° and the composition $C_{13}H_{10}O_7$ and was obviously the free enolic form corresponding to the yellow enolate (X, R = Na); its aqueous solution showed the characteristic reaction of enols (a red-violet colour with ferric chloride), and it added bromine. It could generally be recrystallised unchanged from water. Once, however, during the crystallisation it changed into an isomeric, colourless substance, m. p. 176°, evidently the corresponding lactonic form (X*a*). Subsequently it was found that the aqueous solution contained the two isomerides in equilibrium. On heating the solution the equilibrium was displaced in the direction of the enolic form, as shown by a deepening of the yellow colour. On cooling, the colour again became faintly yellow. From the aqueous solution the yellow or the colourless isomeride could be obtained by inoculation with one or the other. Both isomerides were reconverted into (VI) by concentrated sulphuric acid.

From the formula of the dehydrated adduct (VI) it would appear that no reaction should take place with diazomethane. The substance did, however, react, giving an intensely yellow crystalline substance, sparingly soluble in ether. The reaction with diazomethane must therefore be induced by an enolisation just as in the action of sodium carbonate, and the yellow substance must be the *methyl ether* (IX, R = Me) corresponding to the blood-red sodium salt. The presence of the double bond developed by the enolisation could not be proved directly in this methyl ether, but, as soon as the acid anhydride ring was opened, the unsaturated character of the compound became evident. The opening of the ring was achieved by boiling with methanol. By subsequent treatment with diazomethane, the *dimethyl* ester of the methyl ether (X, R = Me) was formed. This ester was practically colourless, with only a tinge of yellow. In the molten state, however, it had a marked yellow colour. In conformity with the structure (X, R = Me) the ester added two atoms of hydrogen on catalytic hydrogenation. It rapidly took up two atoms of bromine, with loss of 1 mol. of hydrogen bromide, so the resulting *product* had the composition $C_{16}H_{15}O_7Br$. Apparently it is the hydrogen atom in the CH group which has thus been replaced by bromine, but this has not yet been verified.

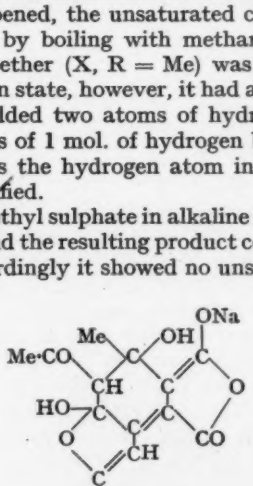
Another *ester*, $C_{17}H_{20}O_8$, was obtained by methylating (VI) directly with methyl sulphate in alkaline solution. Underthese conditions both the lactonic and the anhydride ring were opened, and the resulting product contained four methoxyl groups. It must be the fully methylated ester (XI), and accordingly it showed no unsaturated character.



(XI.)



(XII, light yellow.)



(XIII, violet.)

The same ester was also obtained from the yellow substance (X, R = H) and the isomeric, colourless substance (X*a*). Both these substances gave with diazomethane the same dimethoxy-compound which reacted readily with methanol. By treatment of the product of the latter reaction with diazomethane (XI) was formed. As (X, R = H) is probably an enol, this result was unexpected, and is being further examined.

A special interest is attached to the colour phenomenon accompanying the dissolution of the adduct in weak alkali. The pulverised adduct dissolved rapidly in dilute sodium carbonate solution, giving at first a faintly yellow solution. In the course of ¼ minute or more, depending on the concentration of the sodium carbonate, the solution gradually became violet, this colour deepening in 20—30 mins. and then diminishing slowly during several days. The violet solution became dirty yellow when acidified, and immediately turned violet again when sodium carbonate was added. On the basis of the formula (VIII) for the adduct, these changes may be

interpreted in the following way. The dissolution is caused by enolisation. At first a mono-enolate (XII) is formed, which in solution is light yellow. Gradually a second enolisation sets in, resulting in the formation of the violet dienolate (XIII), which contains a system of crossed conjugated double bonds and so is strongly coloured. When mineral acid is added to the violet solution, the corresponding dirty yellow dienol is liberated.

As the second step of the enolisation proceeds more slowly than the first, the process can be carried through in two stages. On shaking the finely pulverised adduct with a small quantity of dilute sodium carbonate, the mono-enolate is rapidly formed, but, as there is not sufficient alkali for the second stage, the solution remains light yellow (with perhaps a tinge of violet). Only after more sodium carbonate has been added to the yellow solution, from which the excess of adduct has been filtered off, does the solution gradually turn violet. Obviously only a small part of the adduct undergoes enolisation. In the greater part both the rings are most certainly opened by the action of the alkali.

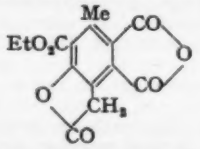
The existence of the enolic forms was proved by means of the ferric chloride reaction. A few seconds after the sodium carbonate had been added, the colour of the solution still being only light yellow, the solution was acidified and ferric chloride added. A light red-violet colour indicated the presence of an enol. After treatment of the violet solution of the dienolate in the same way, a deeper red-violet colour appeared. It was also established that the formation of the enolic forms depended upon the existence of the acid anhydride ring, since the hydrated adduct did not give any colour with alkali or with ferric chloride.

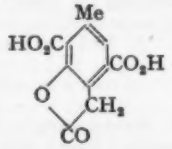
The fact that the adduct reacts with diazomethane, although it contains no free carboxyl group, may obviously be due to its ability to pass into enolic forms. When the finely pulverised adduct was added to an ethereal solution of diazomethane, a slow reaction took place by which about one quarter of the adduct was converted into a crystalline substance (*A*), sparingly soluble in ether, while the remainder (*B*) dissolved completely during the reaction. The *substance* (*A*) had the composition $C_{15}H_{16}O_8$ and contained two methoxyl groups. It may be the dimethyl ether corresponding to the violet enolate (XIII), but this is not yet proved. At present it can only be stated that (*A*) reacted with methanol and then with diazomethane, giving a *trimethoxy*-compound $C_{16}H_{20}O_9$, m. p. 146°, most probably the trimethyl ester of the acid arising from the adduct when both the anhydride and the lactonic ring were opened. The remainder (*B*) also reacted first with methanol and then with diazomethane. In this way a mixture of a colourless, crystalline substance and a dark orange-coloured, viscous liquid was obtained. The former (m. p. 109° after recrystallisation from methanol) also contained three methoxyl groups. It had, however, the composition $C_{17}H_{22}O_9$ and must therefore be a *homologue* of the above ester, m. p. 146°. This noteworthy result, *viz.*, that the action of diazomethane leads to the introduction of a methyl group which cannot be split off by the Zeisel–Fanto reaction, will be studied further. The orange-coloured liquid will also be examined more closely.

Ethyl acetoacetate also reacted with maleic anhydride in the same way as acetylacetone. The crystalline *adduct*, $C_{14}H_{14}O_9$ (VIII, but with CO_2Et for COMe), behaved like that obtained from acetylacetone, apart from the fact that on hydrogenation it absorbed only two atoms of hydrogen. For instance, it lost 2 mols. of water by treatment with sulphuric acid, resulting in formation of an aromatic compound, which dissolved in aqueous sodium carbonate with the same blood-red colour as the acetylacetone adduct, and from which similar derivatives could be prepared. These derivatives are analogous to those obtained from acetylacetone, but have a carbethoxy- instead of an acetyl group, and this difference accounts for the absorption of two hydrogen atoms less.

When the dehydrated adduct (XIV) from ethyl acetoacetate was boiled with hydriodic acid, it gave a mixture of $C_{10}H_8O_4$ (VII), obtained from acetylacetone, and a substance $C_{11}H_8O_6$ (XV), which, on prolonged boiling with hydriodic acid, gave (VII). The substance (XV) contained one carboxyl group more than (VII) and represented the primary product of the decarboxylation. As (XV) did not give an acid anhydride, the two carboxyl groups in the benzene nucleus could not be adjacent and consequently must be situated as shown in (XV).

(XIV.)





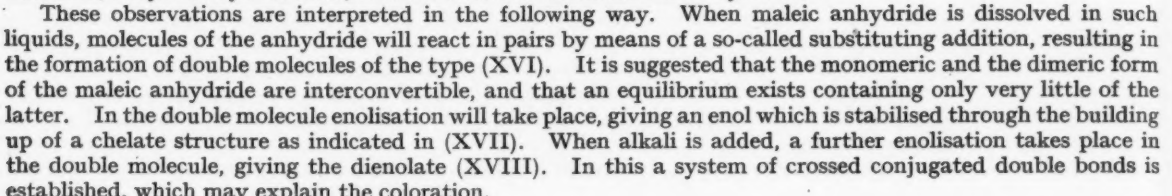
(XV.)

It remains to be explained how one molecule of acetylacetone (or ethyl acetoacetate) can react with two molecules of maleic anhydride to give an adduct with the constitution given above. From the formula (VIII) it is clear that a carboxyl group of one of the maleic anhydride molecules has been directly involved in the formation of the six-membered ring. This suggested that the first step in the reaction was a linking together of the two anhydride molecules to a double molecule (XVI). In this double molecule enolisation will take place, resulting in formation of a pair of conjugated double bonds (XVII). In the second stage of the reaction the enolic form of acetylacetone serves as a dienophilic component and is added to the double molecule of maleic anhydride.

A chance observation apparently justifying the suggestion of a primary formation of a double molecule of the maleic anhydride is that when dilute alkali was added to a solution of maleic anhydride in acetylacetone a light red to brown colour appeared for a shorter or longer time according to the conditions of the experiment. It made no difference if the anhydride was first dissolved in anhydrous methanol and the acetylacetone then added. If, however, the anhydride was dissolved in water before the acetylacetone was added, alkali produced

no colour. Ethyl acetoacetate behaved in the same way as acetylacetone, and it was even found that solutions of maleic anhydride in some other organic liquids gave a light red colour when alkali was added, although these liquids did not react with maleic anhydride under the same conditions as acetylacetone or ethyl acetoacetate. As examples of such liquids can be mentioned the esters of methyl- and dimethyl-acetoacetic acid, ethyl malonate, ethyl methylmalonate, and the esters of methanetricarboxylic acid.

These observations are interpreted in the following way. When maleic anhydride is dissolved in such liquids, molecules of the anhydride will react in pairs by means of a so-called substituting addition, resulting in the formation of double molecules of the type (XVI). It is suggested that the monomeric and the dimeric form of the maleic anhydride are interconvertible, and that an equilibrium exists containing only very little of the latter. In the double molecule enolisation will take place, giving an enol which is stabilised through the building up of a chelate structure as indicated in (XVII). When alkali is added, a further enolisation takes place in the double molecule, giving the dienolate (XVIII). In this a system of crossed conjugated double bonds is established, which may explain the coloration.



This explanation of the reaction of maleic anhydride with acetylacetone (or ethyl acetoacetate) must be regarded as a working hypothesis, and further investigations will be necessary in order to prove its correctness. The author has, however, found it appropriate to publish his results at this stage.

Experimental.

(Temperatures are uncorrected.)

Acetylacetone and Maleic Anhydride.—A lightly closed vessel containing acetylacetone (50 g.; 0·5 mol.) and maleic anhydride (98 g.; 1 mol.) was placed in an oven at 75°. After two weeks a compact and hard crystal cake had been formed. As the cake was very difficult to remove, it was more convenient to inoculate the solution a few days after the heating had started with crystals of the adduct and then stir it from time to time with a glass rod. In this way a paste of small crystals and a brown mother liquor were obtained. It was diluted with ethyl acetate (or ether) and filtered and the crystals were washed with the same solvent until colourless. Yield, 60—70%.

The reaction proceeded even at room temperature, although very slowly: a solution of maleic anhydride (19·6 g.) in acetylacetone (10 g.) in a closed vessel began to deposit crystals in about 40 days, and after 1½ years 18 g. of the adduct (62% of the theoretical) had been formed.

For most purposes the crude, washed product was pure enough. Purification was effected by powdering, and digestion with hot ethyl acetate. For analysis it was recrystallised from ethyl acetate; m. p. 180° (decomp.) (Found: C, 52·55; H, 4·2. $C_{13}H_{12}O_8$ requires C, 52·7; H, 4·1%). The *adduct* (VIII) could not be titrated directly, because of the violet colour which occurred when dilute alkali was added. An excess of 0·2N-sodium hydroxide was therefore rapidly added; after the substance had dissolved completely phenolphthalein was added, and the excess of alkali titrated (Found: *M*, as a tribasic acid, 297·8. $C_{13}H_{12}O_8$ requires *M*, 296·2). 5 G. in anhydrous methanol (50 c.c.) with platinic oxide (0·2 g.) absorbed 778 c.c. of hydrogen in the course of two days (Calc. for 4 atoms of hydrogen: 757 c.c.).

The adduct was practically insoluble in ether, benzene, carbon disulphide, and chloroform, but dissolved in hot acetone. The solution in ethyl acetate did not add bromine. When the adduct was boiled with water it slowly dissolved. A freshly prepared aqueous solution evidently contained an enolic form, since it gave a red-violet colour with ferric chloride, and added bromine. The solution was also coloured light violet by the addition of alkali. When, however, the aqueous solution had been heated for some time on the water-bath, practically no coloration occurred either with alkali or with ferric chloride and very little bromine was added. This was due to the opening of the acid anhydride ring, and the fully hydrated adduct gave no reactions for enols. A crystalline *monohydrate* was prepared by evaporating a solution of the adduct in alkali to which sulphuric acid had been added; after recrystallisation from water it had m. p. 194° (becoming violet at about 175°) (Found: C, 49·55; H, 4·55; *M*, by titration as a tribasic acid, 315·4. $C_{13}H_{14}O_9$ requires C, 49·7; H, 4·5%; *M*, 314·2).

The alkaline solution of the adduct was easily oxidised by potassium permanganate, but no definite oxidation product could be isolated.

Acetylacetone Adduct and Diazomethane.—To an ethereal solution of diazomethane, prepared from nitrosomethylurethane, finely pulverised adduct (8 g.) was added in small portions. A slow reaction started, and in a short time crystals separated. The reaction was promoted by shaking and stirring with a glass rod, and finally the whole was left overnight in an ice-chest. After being separated, washed with ether, and dried in a vacuum, the insoluble *product* (2 g.) had m. p. 148—150° [Found: OMe, 19·2. $C_{13}H_{10}O_6(OMe)_2$ requires OMe, 19·15%].

This solid reaction product dissolved completely when shaken for 3 days with methanol at room temperature. Usually, however, the reaction was carried out by heating for 2 hours on the water-bath. The solution in methanol reacted vigorously with diazomethane. By evaporation of the solution a crystalline product (2·1 g.) was obtained, which by recrystallisation from methanol gave short prismatic crystals, m. p. 146°. Sometimes the recrystallisation would give fine needles with practically the same m. p. This was obviously a labile, dimorphic form, for if the mother-liquor with the crystals was left for some time the fine needles disappeared, and the prismatic crystals were formed. The needles or the prismatic crystals could also be obtained at will from the same solution by inoculating it with one form or the other [Found: C, 54·15; H, 5·75; OMe, 26·6. $C_{13}H_{11}O_6(OMe)_2$ requires C, 53·95; H, 5·65; OMe, 26·15%].

The ethereal mother-liquor from the compound of m. p. 148—150° gave on evaporation a yellow syrup, the colour being intensified when the syrup was heated with 50 c.c. of methanol on the water-bath for 3 hours. After addition of excess of diazomethane and evaporation of the solvent, an orange syrup was left from which 2·35 g. of a colourless, crystalline *substance* separated. Recrystallised from ethanol, it had m. p. 109° [Found: C, 55·2; H, 6·0; OMe, 25·05. $C_{14}H_{13}O_6(OMe)_3$ requires C, 55·15; H, 6·0; OMe, 25·15%].

That part of the orange syrup which did not crystallise has not yet been examined more closely.

Dehydration of the Acetylacetone Adduct.—The adduct (20 g.) was dissolved in concentrated sulphuric acid (90 c.c.), the temperature being kept below 40°. After ½ hour the clear, yellowish solution was poured slowly into ice–water, with vigorous stirring. The dehydrated *product* (VI) separated as a fine, amorphous powder which, after the suspension had been stirred for ½ hour, was collected, washed, and dried in a vacuum. It was thus obtained as a white, light powder (14·7 g.) which could be used directly for most reactions; for analysis it was crystallised from methylal, ethyl acetate, or toluene; needles, m. p. 217—218° (Found: C, 59·9; H, 3·15; *M*, by titration as a tribasic acid, 263·8. $C_{12}H_8O_6$ requires C, 60·0; H, 3·1%; *M*, 260·2). It was insoluble in water at room temperature, but dissolved slowly on boiling, giving a faintly yellow solution, which was coloured red-violet by ferric chloride; it also added bromine. From this aqueous solution the substances (X) could be obtained. In cold methanol and ethanol substance (VI) was slightly soluble, giving yellow to yellow-red solutions from which it could not be recovered by evaporation. In acetone it dissolved with a yellow-red colour and crystallised unchanged on evaporation. In pyridine it dissolved easily with a dark red colour; on addition of acetic anhydride to this solution, the colour became dark brown but no acetylation product could be isolated.

Action of Alkali on (VI).—The colour reactions of this substance have been described on p. 1053. The *compound* (X, R = H), prepared as there described and recrystallised from water, had m. p. 160° (Found: C, 56·15; H, 3·95; *M*, by titration as a tribasic acid, 284·6. $C_{12}H_{10}O_7$ requires C, 56·1; H, 3·6%; *M*, 278·2). The isomeric *compound* (X*a*) had m. p. 176° (Found: C, 56·1; H, 3·7%; *M*, 278·3).

Both these substances gave with diazomethane the same colourless, crystalline *dimethoxy*-derivative, slightly soluble in ether, m. p. 148—150° [Found: C, 58·95; H, 4·6; OMe, 20·35. $C_{12}H_8O_5(OMe)_2$ requires C, 58·8; H, 4·6; OMe, 20·25%]. When shaken for 3 days at room temperature with methanol, it dissolved, and on evaporation of the solvent in a vacuum desiccator over concentrated sulphuric acid, a colourless syrup was obtained; in the course of some weeks this turned into a solid mass, identical with the original substance, m. p. 148—150°, the methanol evidently having reacted and been removed again. However, if diazomethane was added to the solution in methanol, a vigorous reaction took place, resulting in the formation of the fully methylated *substance* (XI). The same product could also be obtained by methylating the dehydrated adduct directly with methyl sulphate in the presence of alkali. It was purified by crystallisation, first from dilute ethanol and then from light petroleum; m. p. 74° [Found: C, 57·85; H, 5·65; OMe, 35·05. $C_{12}H_8O_4(OMe)_4$ requires C, 57·95; H, 5·7; OMe, 35·25%].

Action of Diazomethane on (VI).—The finely powdered substance (2 g.) was added in portions to excess of a vigorously stirred ethereal solution of diazomethane. A slow reaction set in and soon the intensely yellow *substance* (IX, R = Me) began to separate. The mixture was left overnight, and the compound separated and washed with ether; 1·6 g. were obtained, and a little more was got from the mother-liquor. Recrystallised from benzene, it had m. p. 198° [Found: C, 61·1; H, 3·9; OMe, 10·95. $C_{12}H_7O_5(OMe)$ requires C, 61·3; H, 3·7; OMe, 11·3%]. Its solution in benzene did not react with bromine. In boiling methanol the substance was slightly soluble and crystallised rapidly on cooling. If left for a day or two in the mother-liquor, the crystals dissolved, and the yellow colour disappeared, obviously owing to the opening of the acid anhydride ring. Such a solution added bromine. For purpose of further methylation the substance (IX, R = Me) (4 g.) was refluxed for 6 hours with anhydrous methanol (150 c.c.). The bulk of the methanol was distilled off, and after the syrupy residue had been diluted with ether, an ethereal solution of diazomethane was added. When the lively reaction had terminated, the solution was evaporated to dryness in a vacuum desiccator, leaving a crystalline mass; after being washed with cold methanol, this (3·55 g.) was recrystallised from methanol and obtained as nearly colourless crystals, m. p. 137° to a yellow liquid. This substance was obviously *methyl 7-acetyl-2-methoxy-6-methylbenzfuran-4 : 5-dicarboxylate* (X, R = Me) [Found: C, 60·0; H, 5·1; OMe, 29·0. $C_{12}H_7O_4(OMe)_3$ requires C, 60·0; H, 5·05; OMe, 29·05%]. On catalytic hydrogenation this ester readily absorbed hydrogen.

Dissolved in carbon tetrachloride, (X, R = Me) reacted with bromine, evolving hydrogen bromide. Evaporation of the solvent in a vacuum desiccator over paraffin–vaseline afforded a syrupy *bromo*-compound, which was heated for an hour at 80° (Found: Br, 19·7. $C_{16}H_{15}O_7Br$ requires Br, 20·0%).

Action of Hydriodic Acid on (VI).—The compound (VI) (10 g.) was heated for 7 hours with hydriodic acid (*d* 1·7; 120 c.c.) to which some red phosphorus had been added. Carbon dioxide and acetic acid were evolved, and a crystalline substance gradually separated. Next day the product was separated and washed with cold water. It was then dissolved in ether, in which it was only slightly soluble, the solution shaken with aqueous sodium thiosulphate and with water, and dried (Na_2SO_4). After the ether had been distilled off, the residue (5·5 g.) was crystallised from ethanol forming *6-methyl-isocoumaranone-4-carboxylic acid* (VII), m. p. 249° (Found: C, 62·6; H, 4·2; *M*, by titration as a dibasic acid, 191·7. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%; *M*, 192·2). It contained one free carboxyl group and reacted with diazomethane giving a crystalline *methyl* ester which, recrystallised from ethanol, had m. p. 164° (Found: C, 64·1; H, 4·85; OMe, 14·9. $C_{11}H_{10}O_4$ requires C, 64·05; H, 4·9; OMe, 15·05%).

When the acid (VII) was dissolved in 0·2N-aqueous sodium carbonate, the lactone ring was not opened, and the acid was reprecipitated immediately on addition of mineral acid, but when it was dissolved in sodium hydroxide solution, it gave a yellow solution with green fluorescence. The colour and the fluorescence disappeared quickly and the solution became only slightly coloured. On addition of hydrochloric acid to this solution, scratching afforded *5-hydroxy-3-carboxy-p-tolueneacetic acid* (III*a*) (Found: C, 57·1; H, 4·8. $C_{10}H_{10}O_6$ requires C, 57·15; H, 4·8%) as a white, crystalline powder; this had the same m. p. 249° as the lactone, presumably because it lost water during the heating. It could be crystallised from water.

On treatment with diazomethane, the acid (III*a*) was converted into its *dimethyl* ester, the hydroxyl group being unaffected; recrystallised from dilute ethanol, this cleared at 88° but had no sharp m. p. [Found: C, 60·65; H, 5·95; OMe, 25·6. $C_{10}H_8O_3(OMe)_2$ requires C, 60·9; H, 5·9; OMe, 26·05%]. This ester had a tendency to split off one molecule of methanol, giving the ester of the lactonic form (VII); *e.g.*, distillation in a high vacuum afforded a mixture of this lactonic form with unchanged dimethyl ester. Also during an abortive attempt at catalytic hydrogenation of the dimethyl ester dissolved in methanol, the lactonic ester, m. p. 164°, was obtained on evaporation.

The complete methylation of (III*a*) was achieved by shaking its alkaline solution with an excess of sodium hydroxide and methyl sulphate. The product, *methyl 3-carbomethoxy-5-methoxy-p-tolueneacetate*, separted as an oil which solidified on cooling; crystallised from dilute ethanol, it had m. p. 82° [Found: OMe, 36·5. $C_{10}H_7O_3(OMe)_3$ requires OMe, 36·9%]. When this was boiled with aqueous sodium hydroxide, it afforded the *methoxy-acid*; crystallised several times from dilute ethanol, this had m. p. 206° [Found: C, 58·7; H, 5·45; OMe, 13·75. $C_{10}H_9O_4(OMe)$ requires C, 58·9; H, 5·4; OMe, 13·85%].

Decarboxylation of (III*a*).—The acid (III*a*) (16·5 g.) was converted into the sodium salt, mixed with twice its weight of calcium hydroxide and some sand, and in three portions heated electrically in a glass tube connected with a receiver which was cooled in a mixture of ice and hydrochloric acid. The distillate (6·5 g.) consisted of a dark oil which partly crystallised. On redistillation, the main fraction (4·3 g.) boiled at 203—210° and had a phenolic odour. After being kept in an ice-chest, the crystalline part was filtered off, pressed on porous porcelain, and twice crystallised from petrol; it had m. p. 75·5°, and in admixture with *p*-xylenol (m. p. 76°), it had m. p. 76° (Found: C, 78·4; H, 8·35. Calc. for $C_8H_{10}O$: C, 78·65; H, 8·25%). Its oxalate, prepared by Bischoff and von Hedenström's method (*Ber.*, 1902, **35**, 3443),

had m. p. 110° (lit. 111°), and no *m*-xylenyl oxalate could be isolated from either the solid or the liquid part of the distillate.

Oxidation of 3-*Carboxy*-5-*methoxy*-p-*tolueneacetic Acid*.—To a solution of the acid (5 g.) in 25 c.c. of 2N-sodium hydroxide and 200 c.c. of water, 5% aqueous potassium permanganate was added slowly, with vigorous stirring, the temperature gradually rising to *ca.* 80°. When 130 c.c. had been added, the manganese dioxide was filtered off, and the clear solution evaporated on the water-bath to about 100 c.c. Addition of 15 c.c. of 5N-sulphuric acid precipitated 4 g. of a fine white powder. It was crystallised several times from water in which it was sparingly soluble at room temperature; in most cases it formed small, clear prisms, m. p. 242°, but occasionally it separated as a labile, dimorphic form in fine needles [Found: C, 52·3; H, 4·15; OMe, 12·1; *M*, by titration as tribasic acid, 255·8. $C_{10}H_7O_6(OMe)$ requires C, 51·95; H, 3·95; OMe, 12·2%; *M*, 254·2]. This 2-*methoxy*-4 : 6-*dicarboxyphenylacetic acid* (IV, R = Me), on methylation by means of diazomethane, gave a *trimethyl* ester which, purified by crystallisation once from dilute ethanol and twice from petrol, had m. p. 94° [Found: C, 57·2; H, 5·5; OMe, 41·6. $C_{10}H_4O_3(OMe)_4$ requires C, 56·75; H, 5·45; OMe, 41·9%].

Demethylation of (IV, R = Me) was achieved by boiling it with 20 times its weight of hydriodic acid (*d* 1·7) in presence of a little red phosphorus. On cooling, crystals separated which, when crystallised from water, dried, and sublimed in a high vacuum, afforded by loss of $1H_2O$ iso*coumaranone*-4 : 6-*dicarboxylic acid* (V) which had no definite m. p. (Found: C, 54·3; H, 2·65. $C_{10}H_6O_6$ requires C, 54·05; H, 2·7%).

Further Oxidation of (IV, R = Me) *with Nitric Acid*.—To a boiling solution of (IV, R = Me) (3 g.) in 120 c.c. of water, 30 c.c. of nitric acid (*d* 1·4) were added in small portions. The boiling was continued for 2½ hours, and the solution then concentrated on the water-bath to about half its volume. Next day, 1·8 g. of crystals had separated, and another 0·3 g. was obtained by further evaporation of the mother-liquor. After crystallisation from glacial acetic acid, in which it was only slightly soluble, the oxidation product had m. p. 252°; it was 3-*methoxybenzene*-1 : 2 : 5-*tricarboxylic acid* [Found: C, 50·0; H, 3·5; OMe, 12·65; *M*, by titration as a tribasic acid, 242·5. $C_9H_5O_6(OMe)$ requires C, 50·0; H, 3·35; OMe, 12·9%; *M*, 240·2].

2-Methoxybenzene-1 : 3 : 5-tricarboxylic acid has m. p. 248° (Ullmann and Brittner, *Ber.*, 1909, **42**, 2543), but it was different from the above acid, m. p. 252°, for the *trimethyl* ester of the latter, after crystallisation from ethanol, had m. p. 144° [Found: OMe, 43·7. $C_9H_3O_3(OMe)_4$ requires OMe, 43·95%], whereas that of the acid of m. p. 248° has m. p. 86°.

That the tricarboxylic acid contained two adjacent carboxyl groups was evident from the fact that, on sublimation in a high vacuum, it gave an *anhydride*, m. p. 254° (Found: C, 54·15; H, 2·65. $C_{10}H_6O_6$ requires C, 54·05; H, 2·7%).

Ethyl Acetoacetate and Maleic Anhydride.—The reaction between ethyl acetoacetate and maleic anhydride was carried out under the same conditions as described for acetylacetone, and was slow at room temperature. The adduct, crystallised from either ethyl acetate or methylal–benzene, had m. p. 157° [Found: C, 51·45; H, 4·4; OEt, 13·75; *M*, by titration as a tribasic acid, 328·5. $C_{13}H_9O_8(OEt)$ requires C, 51·55; H, 4·35; OEt, 13·8%; *M*, 326·3]. This was rather more soluble than its analogue (VIII) in boiling water, but the solution gave only a faintly red-violet coloration with ferric chloride. It gave, however, a violet-coloured solution when treated with aqueous sodium carbonate, and this solution behaved in the same way as the violet solution of the acetylacetone adduct.

By catalytic hydrogenation 3 g. of adduct took up 238 c.c. of hydrogen at N.T.P. (Calc. for 2H : 227 c.c.).

Dehydration of the adduct was carried out as described in the previous case. The dehydrated product, 7-*carbethoxy*-6-*methyl*iso*coumaranone*-4 : 5-*dicarboxylic anhydride* (XIV), crystallised from benzene, had m. p. 180° (Found: C, 57·5; H, 3·65. $C_{14}H_{10}O_7$ requires C, 57·95; H, 3·45%); it dissolved in aqueous sodium carbonate with a dark red colour, which in this case more rapidly turned yellow. When it (14 g.) was boiled for 4 hours with 140 c.c. of hydriodic acid (*d* 1·7) and a little red phosphorus, crystals separated on cooling overnight; these were filtered off and treated as on p. 1057. Distillation of the ether afforded 10·5 g. of a crystalline substance, which melted very unsharply at 225—240°. It was recrystallised by dissolving it in ethanol and adding water. The first fraction had m. p. 246°, and the second m. p. 250—270°. On recrystallisation the first fraction had m. p. 249°, and was identical with (VII) described above (Found: C, 62·7; H, 4·2%; *M*, by titration as a dibasic acid, 190·3). Addition of mineral acid to the alkaline solution of this acid precipitated the hydroxy-acid (III*a*) (Found: C, 57·05; H, 4·95%). Both (III*a*) and (VII) showed the relationship described on p. 1053.

The fraction, m. p. 250—270°, was purified first by dissolving it in alkali and reprecipitation with sulphuric acid, and then by crystallisation from dilute ethanol, giving a substance, m. p. 295° (Found: C, 51·9; H, 4·15; *M*, by titration as a tribasic acid, 252·1. $C_{11}H_{10}O_7$ requires C, 51·95; H, 3·95%; *M*, 254·2). This substance was 3-*hydroxy*-2 : 5-*dicarboxy*-p-*tolueneacetic acid*, and it was converted by sublimation in a high vacuum into the corresponding 6-*methyl*-iso*coumaranone*-4 : 7-*dicarboxylic acid* (XV) (Found: C, 56·2; H, 3·55. $C_{11}H_8O_6$ requires C, 55·95; H, 3·4%).

This investigation was carried out with some interruption during the last six years. The author is indebted to Nansenfondet and to Det Videnskapelige Forskningsfond av 1919 for several grants.

Many of the analyses have been carried out by the assistants Rasmus Alm, Kåre Fossan, and Brynjulv Kløve, to whom the author gives his warm thanks.

DEPARTMENT OF ORGANIC CHEMISTRY, THE UNIVERSITY, BLINDERN BY OSLO. [*Received, March 6th*, 1946.]

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234. *The Preparation of 4-Aminophenyl Sulphones. Part II. The Reaction between 4-Acetamidobenzenesulphinic Acid and Aromatic Nitroso-compounds.*

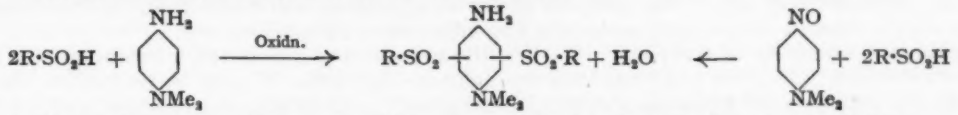
By S. PICKHOLZ.

Hinsberg's explanation of the reaction between aromatic sulphinic acids and *p*-nitrosoalkylanilines is incorrect. Besides a very small amount of a disulphone, which is claimed by Hinsberg as the only product of the reaction, a disulphonamide and a sulphone-sulphonamide are formed as the main products. These three compounds are isomeric. A monosulphonamide, which can also be obtained by hydrolysis of the disulphonamide, is simultaneously formed to a lesser extent. The reaction between the sulphinic acid and *p*-nitrosophenol leads to the formation of the sulphonic acid salt of the same monosulphone as is formed by the oxidation of *p*-aminophenol in presence of the sulphinic acid (see Part I, this vol., p. 685).

IN studies on the reaction between aromatic sulphinic acids and quinones, quinoneimines, or compounds which can produce these by intermediate oxidation, Hinsberg (*Ber.*, 1894, **27**, 3259; 1896, **29**, 2029) put forward the claim that the condensation product formed from two moles of benzenesulphinic acid and one mole of *p*-nitroso-

dimethylaniline was identical with the disulphone formed by the *in situ* oxidation of one mole of *p*-aminodimethylaniline in presence of at least two moles of benzenesulphinic acid.

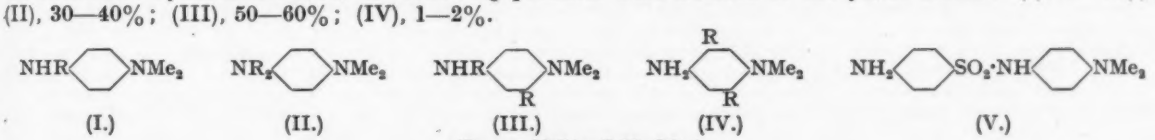
These reactions, which the same author formulated as follows :



were repeated in condensations with 4-acetamidobenzenesulphinic acid. By deacetylation of the condensation products it was hoped to prepare compounds with more than one 4-aminophenyl sulphone group in the molecule and so to extend the work already described in Part I (*loc. cit.*) on unsymmetrical sulphones as potential chemotherapeutic agents, to disulphones containing the essential 4-aminophenyl sulphone structure.

The interaction of the sulphinic acid with the diamine goes probably *via* the mono- to the di-sulphone. An example of this kind is the preparation of 4-*amino*-2 : 5(?)-*bis*-(4′-*acetamidophenylsulphonyl*)-N-*dimethylaniline* (IV) which so far confirms part of Hinsberg's formulation, the orientation of the two sulphone groups being tentatively assumed in accordance with it. The same compound would be expected from the reaction between 4-acetamidobenzenesulphinic acid and *p*-nitrosodimethylaniline. This reaction, however, proved much more complex, and its investigation forms the main part of the present paper. Two publications by Bamberger and Rising (*Ber.*, 1901, **34**, 228, 232) describe the reaction between *p*-toluenesulphinic acid and nitrosobenzene or phenylhydroxylamine. From phenylhydroxylamine not fewer than seven different compounds were isolated, but remarkably enough none of these was related to the products described here. That may be due partly to different conditions for the condensations and partly, as the authors pointed out when comparing their results with Hinsberg's, to the possibility that nitrosobenzene and *p*-nitrosodimethylaniline behave differently.

From the interaction of 4-acetamidobenzenesulphinic acid (2 moles) and *p*-nitrosodimethylaniline (1 mole) in water–alcohol–hydrochloric acid, the following products were isolated in the yields stated : (I), 5—10% ; (II), 30—40% ; (III), 50—60% ; (IV), 1—2%.



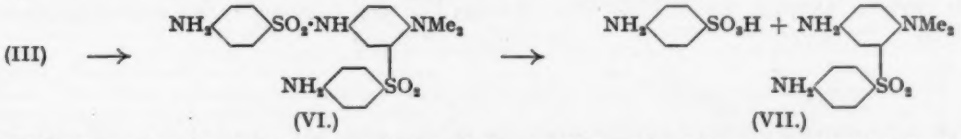
(I.) (II.) (III.) (IV.) (V.)

(R = *p*-NHAc·C_6H_4·SO_2.)

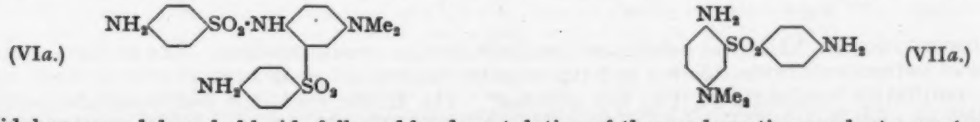
It will thus be seen that the disulphone (IV) (according to Hinsberg the only product) is formed in very small proportion, the main products being the isomeric 4-(*bis*-4′-*acetamidobenzenesulphonyl*)*amino*-N-*dimethylaniline* (II) and 2′-*dimethylamino*-4-*acetamido*-5′-(4″-*acetamidobenzenesulphonamido*)*diphenyl sulphone* (III). The presence of 4-(4′-acetamidobenzenesulphonamido)-*N*-dimethylaniline (I) may be due, at least in part, to secondary formation from (II). The deacetylated 4-(4′-aminobenzenesulphonamido)-*N*-dimethylaniline (V) was actually obtained by prolonged hydrolysis of (II) with simultaneous formation of sulphanilic acid.

The identities of (I), (II), and (V) were established by condensing *p*-aminodimethylaniline with 4-acetamidobenzenesulphonyl chloride to (I) and subsequently causing (I) to react with a second mole of the sulphonyl chloride ; (II) was then formed. Hydrolysis of (I) and (II) gave the same product (V) which had been made previously (Ganapati, *J. Ind. Chem. Soc.*, 1938, **15**, 525) by a method similar to the above sulphonyl chloride condensation.

The constitution of (III), the main product, was established as follows. Deacetylation with hydrochloric acid gave 4-*amino*-2′-*dimethylamino*-5′-(4″-*aminobenzenesulphonamido*)*diphenyl sulphone* (VI), which was split with 50% sulphuric acid at 140—150° to sulphanilic acid and 4 : 5′-*diamino*-2′-*dimethylaminodiphenyl sulphone*



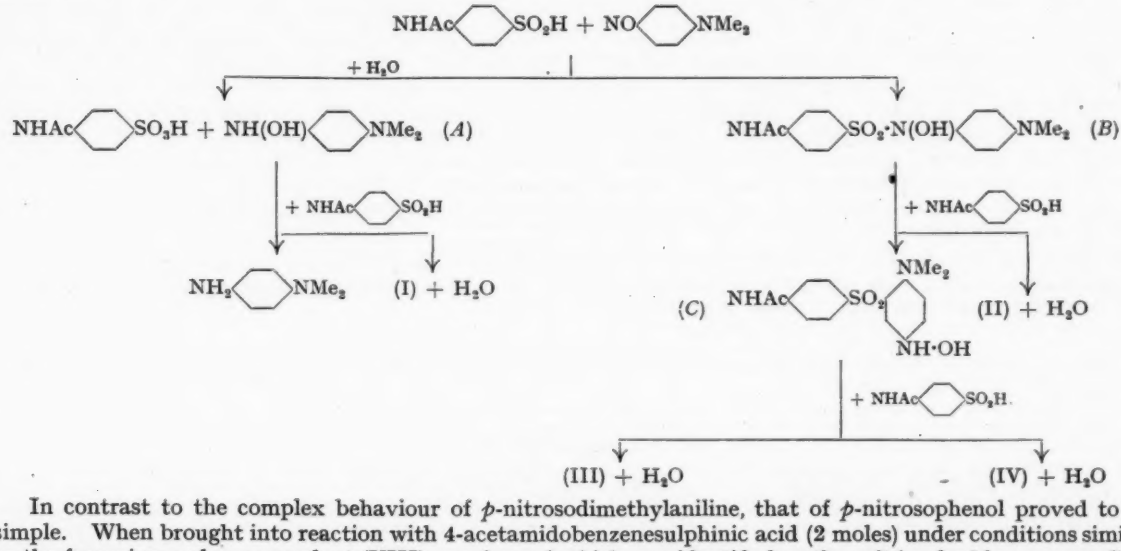
(VII). (VII) is isomeric with 4 : 2′-diamino-5′-dimethylaminodiphenyl sulphone (VII*a*), which had previously been obtained by the intermediate oxidation of *p*-aminodimethylaniline in the presence of 4-acetamidobenzenesulphinic acid and subsequent deacetylation (cf. Part I). Interaction of the acetyl derivative with



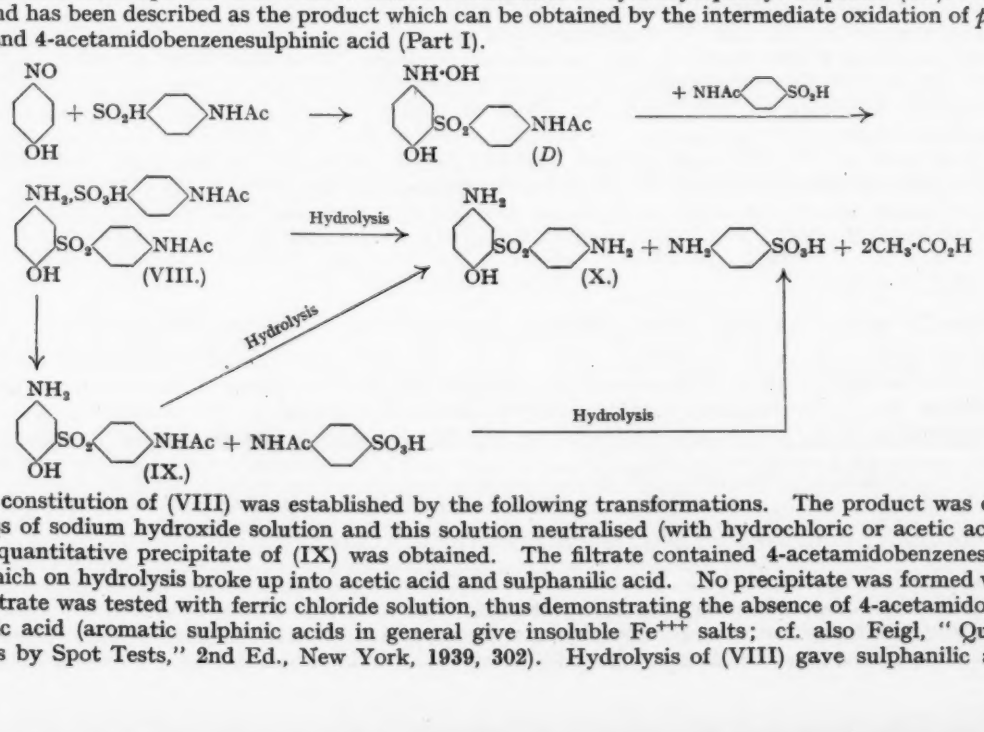
4-acetamidobenzenesulphonyl chloride followed by deacetylation of the condensation product gave 4-*amino*-5′-*dimethylamino*-2′-(4″-*aminobenzenesulphonamido*)*diphenyl sulphone* (VI*a*), isomeric with (VI), thus further demonstrating the related but different constitutions of the isomeric sulphones (VII) and (VII*a*). The structure of (VI) was conclusively established by an independant synthesis. Starting from (V) and oxidising this

substituted *p*-aminodimethylaniline in presence of 4-acetamidobenzenesulphinic acid and deacetylating the condensation product, a substance identical with (VI) was isolated. That the sulphone group had entered the *m*- and not the *o*-position to the amino group [as would have happened with *p*-aminodimethylaniline itself (see Part I)] is presumably due to the presence of the 4-aminophenylsulphonyl group as substituent, which appears to have weakened the normally *ortho* directing influence of the amino-group.

To explain the formation of compounds (I—IV), the hypothetical intermediate formation of *p*-hydroxylaminodimethylaniline (*A*) and its 4-acetamidobenzenesulphone derivative (*B*) may be postulated (see scheme). Interaction of *A* with a second molecule of sulphinic acid gives (I) with elimination of water, and *B* by a similar reaction would lead to (II). *B* may undergo a rearrangement to the sulphone *C*, in the manner proposed by Bamberger and Rising (*loc. cit.*) for the reaction with nitrosobenzene, and then may by subsequent addition of sulphinic acid form the sulphone-sulphonamide (III). A small amount of *C* may be directly reduced by a second molecule of sulphinic acid with simultaneous formation of (IV). The complete reduction of *p*-nitroso- to *p*-amino-dimethylaniline as a further, but in the present discussion unimportant, side reaction may be mentioned.



In contrast to the complex behaviour of *p*-nitrosodimethylaniline, that of *p*-nitrosophenol proved to be simple. When brought into reaction with 4-acetamidobenzenesulphinic acid (2 moles) under conditions similar to the foregoing, only one product (VIII) was formed which was identified as the *salt* (or double compound) of 4-acetamidobenzenesulphonic acid with 5′-amino-4-acetamido-2′-hydroxydiphenyl sulphone (IX). This last compound has been described as the product which can be obtained by the intermediate oxidation of *p*-aminophenol and 4-acetamidobenzenesulphinic acid (Part I).



The constitution of (VIII) was established by the following transformations. The product was dissolved in excess of sodium hydroxide solution and this solution neutralised (with hydrochloric or acetic acid). An almost quantitative precipitate of (IX) was obtained. The filtrate contained 4-acetamidobenzenesulphonic acid, which on hydrolysis broke up into acetic acid and sulphanilic acid. No precipitate was formed when the same filtrate was tested with ferric chloride solution, thus demonstrating the absence of 4-acetamidobenzenesulphinic acid (aromatic sulphinic acids in general give insoluble Fe^{+++} salts; cf. also Feigl, "Qualitative Analysis by Spot Tests," 2nd Ed., New York, 1939, 302). Hydrolysis of (VIII) gave sulphanilic acid and

4 : 5′-diamino-2′-hydroxydiphenyl sulphone (X) which was also obtained by deacetylation of (IX). The formation of (VIII) proceeds probably as follows. *p*-Nitrosophenol combines with one mole of the sulphinic acid to the intermediate (but not isolated) 5′-hydroxylamino-4-acetamido-2′-hydroxydiphenyl sulphone, *D*. This is reduced by a second mole of the sulphinic acid to (IX) which in turn forms with the simultaneously produced 4-acetamidobenzenesulphonic acid the salt (VIII) (see scheme).

Tests for antibacterial activity were carried out with (IV*a*), (V), and (VI) [obtained by deacetylation from (IV), (I), and (III)] as described previously (Part I). (V) was practically non-toxic, and its activity of the order of that of sulphanilamide. (VI), like (VI*a*), was practically devoid of any activity both *in vitro* and *in vivo*. (IV*a*) gave fluctuating but inferior results *in vivo* in comparison with sulphanilamide, while its *in vitro* activity was quite high.

Although it is not claimed at this stage that the reactions described here are general, preliminary experiments appear to show that similar condensations occur with *p*-nitrosodiethylaniline, *p*-nitroso-*o*- and *m*-cresol, and (repeating Hinsberg's experiments) with benzenesulphinic acid. These experiments have had to be temporarily interrupted, but it is hoped to carry them to conclusion later.

Experimental.

4-(4′-*Acetamidobenzenesulphonamido*)-N-*dimethylaniline* (I).—(*a*) The hydrochloride of *p*-nitrosodimethylaniline (Hodgson and Nicholson, *J.*, 1941, 472, 36 g.) was dissolved in dilute hydrochloric acid (10 c.c. in 500 c.c. water) and a suspension of 4-acetamidobenzenesulphinic acid (81 g.) in ethanol (300 c.c.) and water (200 c.c.) added with stirring, the dark brown solution being kept at 35—45°. During the reaction the colour changed, and after 15—20 minutes a clear greenish solution was obtained. After 1 hour, water (300 c.c.) was added; this precipitated a dark green resinous product. The mixture was then adjusted to pH 4—4·5 with dilute ammonia (1 : 5; 100 c.c.). More insoluble material was formed, which was filtered off [mixture of (II) and (III)]. The mother liquors were made alkaline with ammonia (pH 7·3—7·5) and a third precipitate was obtained, filtered off, dried (12·5 g.), and digested in the cold with ethanol (50 c.c.). The dark blue ethanol extract was removed, and the insoluble residue dried and boiled under reflux with 95% ethanol (30 c.c.); the crystals still undissolved (6 g.) were recrystallised twice from 90—95% ethanol, to yield cream coloured crystals (4 g.), m. p. 193—195° (Found: S, 9·5. Calc. for $C_{16}H_{19}O_3N_3S$: S, 9·6%).

(*b*) *p*-Aminodimethylaniline (5 g.) was dissolved in dry pyridine (10 c.c.), and 4-acetamidobenzenesulphonyl chloride (10 g.) dissolved in dry pyridine (25 c.c.) gradually added with stirring. The bluish mixture became warm and was heated for 30 minutes on the steam-bath to complete the reaction. After cooling, glacial acetic acid (25 c.c.) was added, and finally water (50 c.c.), and the mixture left for some hours; it was then almost solid. It was diluted with water (50 c.c.) and the crystals were filtered off. Two recrystallisations from 90% ethanol gave 7—8 g. of cream coloured coarse needles, m. p. 194—195°, giving no m. p. depression with the former product (Ganapati gives m. p. 196°).

4-(*Bis*-4′-*acetamidobenzenesulphonyl*)*amino*-N-*dimethylaniline* (II).—(*a*) 4-Acetamidobenzenesulphinic acid (80 g.) was suspended in water (2000 c.c.) and a solution of the hydrochloride of *p*-nitrosodimethylaniline (33 g.) in water (1000 c.c.) brought into reaction as before. After 4 hours 10% sodium acetate solution (1000 c.c.) was added, and stirring continued for 2 hours longer. The yellowish-green precipitate was collected, washed with water, and dried in a vacuum. This material was stirred for an hour at room temperature with 10% aqueous sodium hydroxide solution (800 c.c.) and the insoluble product filtered off, washed with more sodium hydroxide solution, then thoroughly with water, and dried. The crude material (31 g.) was boiled under reflux with 95% ethanol (150—200 c.c.). After cooling, the insoluble crystals were collected, washed with ethanol, and dried. A sample, recrystallised from ethanol–acetone (2 : 1) gave almost white needles, m. p. 214—216° (decomp.) The *compound* was insoluble in sodium hydroxide solution, not very soluble in dilute acids, cold acetone, or ethanol (Found: N, 10·8; S, 12·3. $C_{24}H_{26}O_6N_4S_2$ requires N, 10·6; S, 12·1%).

(*b*) 4-(4′-Acetamidobenzenesulphonamido)-*N*-dimethylaniline (6 g.) was dissolved in 5% sodium hydroxide solution (20 c.c.) and a solution of 4-acetamidobenzenesulphonyl chloride (5 g.) in acetone (30 c.c.) slowly added with stirring. The mixture was cooled externally and kept alkaline by adding more sodium hydroxide solution when necessary. After 1 hour the mixture was acidified with dilute hydrochloric acid and then diluted with water until a first flocculant precipitate was formed. This was removed and the filtrate diluted with water until no more separated. The substance was collected on the following day, washed with water, dried, and boiled with methanol (100 c.c.). The filtrate was concentrated to about 30—40 c.c. and cooled. On keeping, crystals formed which, after recrystallisation from ethanol–acetone, had m. p. 213—215°, identical with the compound above (4 g.).

Separation of (II) *and* (III).—The yellowish-green precipitate, which was formed by neutralising the above reaction mixture from 4-acetamidobenzenesulphinic acid and *p*-nitrosodimethylaniline, was boiled under reflux in 90% ethanol. After some minutes the dark green solution deposited crystals whilst still hot. The heating was stopped after 20 minutes and the mixture left overnight; the crystals were then collected and washed with ethanol until the washings were colourless. The substance was twice recrystallised from 90% ethanol, giving white needles, m. p. 212—214° (20 g.), identical with (II). Traces of (III) were present and were very difficult to remove by recrystallisation, but were easily separated by treatment with sodium hydroxide solution as described earlier. The alcoholic mother liquors from all crystallisations were combined, concentrated, and left for some days; crops of (II) and (III) were then obtained which were again recrystallised. The whole procedure was rather tedious and unsatisfactory, especially for the separation of (III).

4-(4′-*Aminobenzenesulphonamido*)-N-*dimethylaniline* (V).—(*a*) (I) (5 g.) was deacetylated by boiling it in 10% hydrochloric acid (50 c.c.) for 1 hour. The bluish solution was filtered (charcoal) and the filtrate neutralised with dilute ammonia. The slightly cream coloured precipitate was recrystallised from 90% ethanol; white needles (3 g.), m. p. 228—230° (Ganapati records m. p. 232°) (Found: S, 10·8; N, 14·6. Calc. for $C_{14}H_{17}O_2N_3S$: S, 11; N, 14·4%).

(*b*) The bis-compound (II) (28 g.) was boiled for 2 hours under reflux with 95% ethanol (40 c.c.) and 16% hydrochloric acid (80 c.c.). The solution was cooled overnight in a refrigerator and the crystals (sulphanilic acid 7·2 g.) collected. The mother liquors were decolorised with charcoal and filtered. The filtrate was neutralised with ammonia and a yellowish-green precipitate obtained. This was collected and stirred with 1·5% sodium hydroxide solution (200 c.c.). A small amount of an insoluble yellowish-green substance remained undissolved and was removed (IV*a*). The alkaline filtrate was decolourised with charcoal and after filtration neutralised with acetic acid. The grey precipitate, twice recrystallised from 90% ethanol, gave white needles (14 g.), m. p. 227—229°, identical with the above substance from (I).

2′-*Dimethylamino*-4-*acetamido*-5′-(4″-*acetamidobenzenesulphonamido*)*diphenyl Sulphone* (III).—The alkaline mother liquors from (II) were twice decolorised with charcoal. The yellow filtrate was acidified with dilute acetic acid and the cream coloured precipitate isolated, dried (50 g.), and dissolved in hot 93% ethanol (150—200 c.c.). The dark solution was twice filtered (charcoal) and left overnight. White needles formed which were collected, washed with ethanol and ether, and dried. The *product* had m. p. 245—247° (30—35 g.). It was slightly soluble in stronger acid, easily in sodium

hydroxide solution, not in acetone, ethanol or methanol, difficultly in benzene (Found: S, 12·2; N, 10·9. $C_{24}H_{26}O_6N_4S_2$ requires S, 12·1; N, 10·6%).

4-Amino-2'-dimethylamino-5'-(4''-aminobenzenesulphonamido)diphenyl Sulphone (VI).—(*a*) By deacetylation of (III). Isolation and purification of (VI) were carried out generally as described for (V). No sulphanilic acid was formed. The *product* formed white needles, m. p. 196—198°, soluble in acid and alkaline solutions (Found: S, 14·5. $C_{20}H_{22}O_4N_4S_2$ requires S, 14·3%).

(*b*) 4-(4'-Aminobenzenesulphonamido)-*N*-dimethylaniline (V; 7 g.) was dissolved in 2% hydrochloric acid (1200 c.c.). A suspension of 4-acetamidobenzenesulphinic acid (5 g.) in water (50 c.c.) was added with stirring, the temperature raised to 50—60°, and 10% aqueous ferric chloride (100 c.c.) run in during 15 minutes. A solution was obtained from which tarry material separated after 2 hours. This was removed, the filtrate diluted with an equal volume of water, and a second tarry precipitate collected with the aid of charcoal. The clear filtrate was neutralised with sodium acetate. A partly crystalline product separated, which was collected, washed with water, and dried in a vacuum (4 g.). It was hydrolysed, without further purification, with a mixture of ethanol (10 c.c.) and 10% hydrochloric acid (30 c.c.). After prolonged boiling a brown solution was obtained which was decolourised with charcoal. The filtrate was neutralised with sodium bicarbonate and the precipitate recrystallised 3 times from ethanol; white to cream needles, m. p. 195—198° (1·5 g.). No m. p. depression, when mixed with a sample from (*a*).

4 : 5'-Diamino-2'-dimethylaminodiphenyl Sulphone (VII).—A solution of (VI) (10 g.) in 50% sulphuric acid was heated at about 140—150° for 1 hour. The dark solution was cooled, diluted with water (500 c.c.), and almost neutralised with sodium hydroxide. The precipitate (4 g.) was collected, redissolved in dilute hydrochloric acid, the solution decolourised with charcoal, and the filtrate neutralised with sodium bicarbonate. The precipitate was recrystallised from 95% ethanol and white crystals obtained, m. p. 208—210°. The *compound*, isomeric with (VII*a*), was soluble in acid, but insoluble in sodium hydroxide solution (Found: S, 10·7; N, 14·6. $C_{14}H_{17}O_2N_3S$ requires S, 11; N, 14·4%).

4-Amino-5'-dimethylamino-2-(4''-aminobenzenesulphonamido)diphenyl Sulphone (VI*a*).—To a mixture of 2'-amino-5'-dimethylamino-4-acetamidodiphenyl sulphone (Part I) (6 g.) and dry pyridine (10 c.c.) was added a solution of 4-acetamidobenzenesulphonyl chloride (4·4 g.) in dry pyridine (15 c.c.). The dark solution was heated on the steam-bath for 1 hour. After cooling, it was treated with glacial acetic acid (25 c.c.) followed by water (25 c.c.). Crystallisation began and was completed by dilution with more water (100 c.c.) in portions. The precipitate was collected, washed with water, and recrystallised from 80% aqueous ethanol (150 c.c.) to yield slightly yellow needles, m. p. 234—235° (5·5 g.), of *5'-dimethylamino-4-acetamido-2'-(4''-acetamidobenzenesulphonamido)diphenyl sulphone* [isomeric with (III)] (Found: S, 12·3. $C_{24}H_{26}O_6N_4S_2$ requires S, 12·1%). The acetylated sulphone (3·5 g.) was hydrolysed as usual and the deacetylated product precipitated with dilute ammonia. For purification, it was dissolved in hot acetone, the solution decolourised with charcoal, and the warm filtrate triturated with water until crystallisation began; cream needles, m. p. 218—220° (2·2 g.). The *substance* was soluble in acid and alkaline solutions (Found: S, 14·5; N, 12·8. $C_{20}H_{22}O_4N_4S_2$ requires S, 14·3; N, 12·6%).

4-Amino-2 : 5(?)-bis-(4'-acetamidophenylsulphonyl)-N-dimethylaniline (IV).—To a solution of 2'-amino-5'-dimethylamino-4-acetamidodiphenyl sulphone (6 g.) in 10% hydrochloric acid (100 c.c.) was added a solution of 4-acetamidobenzenesulphinic acid (4 g.) in 50% aqueous ethanol (30 c.c.). 10% Ferric chloride solution (60 c.c.) was added drop by drop with stirring at 50—60°. The mixture at first became cloudy and later a tarry product separated. Stirring was stopped after 1 hour and the supernatant liquid decanted from the precipitate. This was boiled with ethanol (30 c.c.) and changed to yellowish-brown crystals (3·5 g.). A sample, recrystallised from 90% ethanol, formed yellowish needles, m. p. 276—278°, insoluble in acid and in sodium hydroxide solution (Found: S, 12·2; N, 10·8. $C_{24}H_{26}O_6N_4S_2$ requires S, 12·1; N, 10·6%). The same *compound* could be prepared in one step from *p*-aminodimethylaniline in a similar way, using the starting materials in the ratio amine : sulphinic acid : ferric chloride = 1 : 2 : 4, instead of sulphone : sulphinic acid : ferric chloride = 1 : 1 : 2. The first method is, however, preferable.

4-Amino-2 : 5(?)-bis-(4'-aminophenylsulphonyl)-N-dimethylaniline (IV*a*).—(*a*) The foregoing compound (1 g.) was hydrolysed with 10% hydrochloric acid (20 c.c.), the solution diluted with an equal volume of water, and dilute ammonia (1 : 4) added until a slight cloudiness persisted. The solution was clarified with charcoal and the filtrate brought to pH 2·5—3 with more ammonia. Bright yellowish-green crystals precipitated, which were collected and washed with water, methanol, and ether. No further purification was necessary. The *compound* was soluble in strong acids, and in warm acetone, ethanol, or methanol, insoluble in sodium hydroxide solution. Solutions in acetone or ethanol showed a very intense yellowish-green fluorescence, which was extinguished on acidifying the solutions with hydrochloric or sulphuric acid; m. p. 263—264° (0·5 g.) (Found: S, 14·5; N, 12·8. $C_{20}H_{22}O_4N_4S_2$ requires S, 14·4; N, 12·6%).

(*b*) The yellowish-green product which remained undissolved in sodium hydroxide solution [see preparation of (V) from (II)] was purified by dissolving in hot acetone, filtering (charcoal), and slowly concentrating the filtrate. Yellowish-green crystals separated, m. p. 263—265°, not depressed by the disulphone obtained from (*a*).

4-Acetamidobenzenesulphonic Acid Salt of 5'-Amino-4-acetamido-2'-hydroxydiphenyl Sulphone (VIII).—To a suspension of *p*-nitrosophenol (15 g.) in water (300 c.c.) was added 4-acetamidobenzenesulphinic acid (56 g.) partly dissolved in hot water (300 c.c.). The mixture was slowly heated to 85—90° with stirring for 1 hour and the dark solution filtered (charcoal). The filtrate was cooled to about 50—60° and a tarry precipitate removed. The liquors were left with cooling and cream crystals obtained (45—50 g.), which recrystallised from water to give white needles, m. p. 206—208° (decomp.) after having been dried for some hours at 110—120°. The *product* was soluble in hot water, acid, and caustic solutions, but only slightly in ethanol or acetone (Found: S, 12·1; N, 8·2. $C_{32}H_{28}O_8N_2S_2$ requires S, 12·3; N, 8·1%).

5'-Amino-4-acetamido-2'-hydroxydiphenyl Sulphone (IX).—(VIII) (5 g.) was dissolved in excess of cold dilute sodium hydroxide solution and neutralised with acetic acid. A cream precipitate was obtained and recrystallised from ethanol. It had m. p. 233—235° and was identical with the reaction product from *p*-nitrosophenol and 4-acetamidobenzenesulphinic acid (Part I).

4 : 5'-Diamino-2'-hydroxydiphenyl Sulphone (X).—(*a*) (VIII) (4 g.) was boiled with dilute hydrochloric acid (1 : 4; 30 c.c.) for 1 hour and the solution cooled. Sulphanilic acid crystallised out (1·1 g.) and was removed, the filtrate evaporated to dryness, and the residue extracted with hot ethanol; a second crop of sulphanilic acid (0·4 g.) was then collected. The alcoholic mother liquors were concentrated, diluted with water, and decolorised with charcoal. The filtrate was neutralised with ammonia and the precipitate (1·9 g.) further purified by recrystallisation from methanol. The product, m. p. 210—212°, was identical with that previously described (Part I).

(*b*) The same substance was obtained by alkaline hydrolysis of (VIII) and subsequent neutralisation of the solution with acetic acid.

The author wishes to express his thanks to the Directors of Messrs. Ward, Blenkinsop & Co. Ltd. for permission to publish this work.

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235. *Antiplasmodial Action and Chemical Constitution. Part VIII. Guanidines and Diguanides.*

By Harold King and Isabel M. Tonkin.

The aim of this investigation was the development by chemical synthesis of the novel discovery that *p*-tolylguanidine nitrate had a very slight retarding action on a sporozoite-induced infection of *Plasmodium gallinaceum* in chicks. A large number of aromatic and aliphatic guanidines have been synthesised and also a number of aromatic diguanides. The most active compound found was *p*-anisylguanidine nitrate. Many variants of this molecular structure have been made, including all the ten possible *N*-methyl derivatives, without finding anything of superior activity.

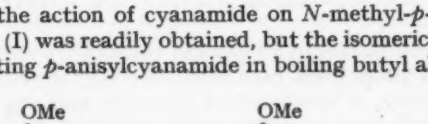
During the progress of a research on substances chemotherapeutically active against experimental typhus in mice (Andrewes, King, van den Ende, and Walker, *Lancet*, 1944, i, 777; Andrewes, King, and Walker, *Proc. Roy. Soc.*, 1946, *B*, **133**, 20) a large number of substances were synthesised for trial. At the end of the investigation it seemed worth while to test many of these compounds which were of comparatively small molecular build, and might therefore be capable of penetrating cells, on a sporozoite-induced infection of *P. gallinaceum* in the chick. Such an infection was known to undergo a tissue-phase development before the blood became infected, and a drug which could control the tissue phase might open up a new avenue in the therapy of human malaria.

At the time the work was undertaken it was known that plasmochin had a very slight action in this type of test (Mudrow, *Arch. Schiff. Trop. Hyg.*, 1940, **44**, 257; cf. however Schulemann, *Deut. med. Woch.*, 1940, **16**, 253) and that sulphadiazine and sulphapyrazine had a most marked action, malaria failing to develop (Coatney and Cooper, *U.S. Public Health Rep.*, 1944, **59**, 1455; Coggeshall, Porter and Laird, *Proc. Soc. Exp. Biol. Med.*, 1944, **57**, 286; Freire and Paraense, *Rev. Brasil Biol.*, 1944, **4**, 27).

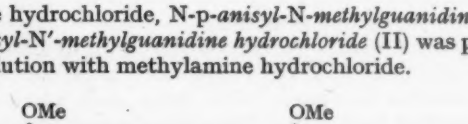
Among the substances tried on experimental typhus we found one, *p*-tolylguanidine nitrate, which had a slight action on sporozoite-induced infections of *P. gallinaceum* in the chick. A large number of aromatic guanidines and the corresponding diguanides were therefore prepared together with a few aliphatic guanidines; of these only *p*-anisylguanidine nitrate was found with definitely superior activity, but it was insufficient to produce cures. The effects of isomerism, of homologation, and of substituents such as chlorine or methoxyl on the *p*-anisylguanidine molecule were then explored. In addition the effect of alkyl substituents on the nitrogen atoms was thoroughly examined by the preparation of all the ten possible *N*-methyl derivatives and a number of higher alkyl derivatives.

In the aliphatic series all the possible *N*-methyl derivatives of guanidine are already known, but nothing comparable is known in the aromatic series so that methods had to be worked out for *N*-methylated aromatic guanidines.

By the action of cyanamide on *N*-methyl-*p*-anisidine hydrochloride, N-p-*anisyl*-N-*methylguanidine hydrochloride* (I) was readily obtained, but the isomeric N-p-*anisyl*-N′-*methylguanidine hydrochloride* (II) was prepared by treating *p*-anisylcyanamide in boiling butyl alcohol solution with methylamine hydrochloride.



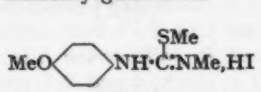
(I.)



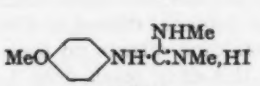
(II.)

This method was also applicable to the preparation of N-p-*anisyl*-N′N′-*dimethylguanidine hydrochloride* and higher alkylated derivatives of similar type. The method would not, however, function with *p*-anisylmethylcyanamide, a mobile hydrogen atom being apparently essential for success, although Bhatnagar, Chopra, Narang, and Ray (*J. Ind. Chem. Soc.*, 1937, **14**, 344) claim to have made *N*-phenyl-*N′N′*-dimethylguanidine by heating aniline hydrochloride and dimethylcyanamide at 110—120°.

To secure the higher *N*-methylated derivatives an application of the method introduced by Wheeler and Jamieson (*J. Biol. Chem.*, 1908, **4**, 111) for the preparation of methyl- and dimethyl-guanidines proved to be quite satisfactory. Thus *p*-anisidine and methyl *iso*thiocyanate gave N-p-*anisyl*-N′-*methylthiourea* which added on methyl iodide to give N-p-*anisyl*-N′S-*dimethylisothiourea hydriodide* (III); this by the action of alcoholic methylamine or dimethylamine at 80° gave N-p-*anisyl*-N′N″-*dimethylguanidine hydriodide* (IV) and N-p-*anisyl*-N′N′N″-*trimethylguanidine hydriodide* (V) respectively, a by-product in the former reaction being *s*-trimethylguanidine.



(III.)



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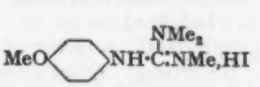
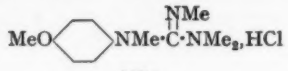


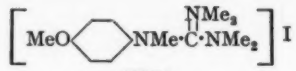
(V.)

In a similar manner N-p-*anisyl*-NS-*dimethylisothiourea hydriodide* gave N-p-*anisyl*-NN′-*dimethylguanidine hydrochloride* and N-p-*anisyl*-NN′N′-*trimethylguanidine hydriodide* whilst N-p-*anisyl*-NN′S-*trimethyl-*

isothiourea *hydriodide* gave N-p-*anisyl*-NN′N″-*trimethylguanidine hydriodide* and N-p-*anisyl*-NN′N′N″-*tetramethylguanidine hydrochloride* (VI).



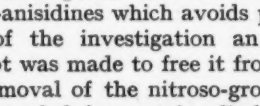
(VI.)



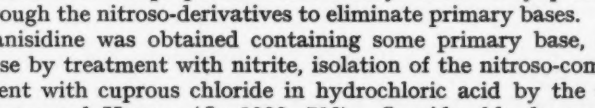
(VII.)

Finally (VI) as base readily added on methyl iodide to yield N-p-*anisyl*-NN′N′N″-*tetramethylguanidine methiodide* (VII).

In the Experimental section a method is described for the preparation of *N*-methyl- and *N*-ethyl-*p*-toluidines and -*p*-anisidines which avoids proceeding through the nitroso-derivatives to eliminate primary bases. At one stage of the investigation an *N*-methyl-*p*-anisidine was obtained containing some primary base, and an attempt was made to free it from primary base by treatment with nitrite, isolation of the nitroso-compound, and removal of the nitroso-group by treatment with cuprous chloride in hydrochloric acid by the method recommended for certain alkylanilines by Jones and Kenner (*J.*, 1932, 713). Considerable decomposition occurred during the cuprous chloride treatment, and during the isolation of the *N*-methyl-*p*-anisidine a monochloro-*N*-methyl-*p*-anisidine was obtained which could be either 2- or 3-chloro-4-methoxy-*N*-methylaniline (VIII or IX).



(VIII.)



(IX.)

To settle the constitution of the new base it would be sufficient to synthesize either of these two isomerides. Hurst and Thorpe (*J.*, 1915, **107**, 938) stated that when *p*-nitrophenetole was reduced under very vigorous conditions with tin and hydrochloric acid a 90% yield of 2-chloro-4-ethoxyaniline was obtained whereas if the reaction was moderated by running water a 50% yield ensued. They stated that the corresponding methoxy-derivative was obtained in a similar way. On repetition of this latter experiment under very vigorous conditions the maximum yield of 2-chloro-4-methoxyacetanilide obtained was below 5%, and the properties of the product agreed with those given by Hurst and Thorpe and by D.R.-P. 621,710. As the small yield precluded the use of this method, attention was turned to the synthesis of the isomeric base. This was readily accomplished by nitrating *o*-chloroanisole to give 2-chloro-4-nitroanisole which on reduction, formylation, and methylation gave eventually 3-*chloro*-4-*methoxy*-N-*methylaniline* (IX) as *hydrochloride* and *picrate*. These salts were quite different from the salts of the chloro-base obtained in the cuprous chloride reaction. This latter base must consequently be 2-chloro-4-methoxy-*N*-methylaniline (VIII), since chlorination of the *N*-methyl or the methoxyl group is unlikely.

Biological Results.—Sporozoite infections of *Plasmodium gallinaceum* in 10-day old chicks were induced by the intravenous injection of a suspension of ground-up infected mosquitoes, each chick receiving the equivalent of one infected mosquito. The drugs were administered orally, 2 hours before infection and twice daily thereafter for 4 days only. The percentage of parasitized red cells in the drug-treated birds was compared with that in the control birds at the peak of parasitæmia. Control chicks usually died two to three days after the peak of parasitæmia as a result of massive infection of the tissues with exoerythrocytic forms. True causal prophylactic action is manifested by a prolongation of life beyond that of the controls and by a retarded infection of the blood-stream.

About 70 guanidines and diguanides including all those mentioned in this paper and a few others derived from α- and β-naphthylamines have been tested in this way. The following compounds showed either a very slight action (+−), a definite action (+), or a pronounced action (++).

		Total dose, mg./100 g. chick.
p-Tolylguanidine nitrate	+−	60
N-*p*-Tolyl-*N*-methylguanidine nitrate	+−	80
o-Xylyldiguanidine hydrochloride	+−	12·5
p-Anisylguanidine nitrate	+	40—80
p-Phenetylguanidine nitrate	+−	25
N-*p*-Anisyl-*N*′-ethylguanidine hydrochloride	+−	100
Sulphadiazine	++	200

The action of *p*-anisylguanidine nitrate on exoerythrocytic forms was confirmed in tissue culture; a 0·5 mg. % solution markedly inhibited the growth of exoerythrocytic forms. (Tonkin, forthcoming publication.)

We are indebted to Dr. D. G. Davey of Imperial Chemical (Pharmaceuticals) Ltd. for confirmation of the causal prophylactic activity of *p*-anisylguanidine nitrate on sporozoite-induced *P. gallinaceum* infections in chicks. He writes " Chicks treated with this drug (each dose 4 mg. per 50 g. chick, dosed 2 hours before inoculation and 2 hours after inoculation and twice daily on each of the next 3 days) did not exhibit parasites in the blood until the 8th day and they did not die until the 11th—14th day. This compound, therefore, shows definite causal prophylactic activity ".

Dr. Ann Bishop, at the Molteno Institute, Cambridge, to whom our thanks are also due, tested *p*-anisyl-

guanidine nitrate against sporozoite and against trophozoite-induced infections of *P. relictum* in the canary. In both types of infection it was without action.

Experimental.

Guanidines.

m-*Chlorophenylguanidine Nitrate.*—*m*-Chloroaniline hydrochloride (4·0 g.) and cyanamide (2·1 g., 2 mols.) were boiled in absolute alcohol (20 c.c.) for 6 hours. The solvent was removed, the residue dissolved in water (10 c.c.), and ammonium nitrate added in excess. The *nitrate* (4·4 g.) readily crystallised out and when recrystallised from water (10 c.c.) separated in columns, m. p. 171—172° (Found: C, 36·0; H, 3·7; N, 24·4. $C_7H_8N_3Cl,HNO_3$ requires C, 36·1; H, 3·9; N, 24·1%).

p-*Bromophenylguanidine Nitrate.*—This *salt* (4·55 g.) was obtained similarly from *p*-bromoaniline hydrochloride (5·2 g.). It separated from water in large columns, m. p. 187—188° (Found: C, 30·5; H, 3·3; N, 20·5. $C_7H_8N_3Br,HNO_3$ requires C, 30·3; H, 3·3; N, 20·2%). The picrate had m. p. 224°; Braun, Erit, and Crooks (*J. Org. Chem.*, 1938, **3**, 146) give picrate, m. p. 220°.

o-*Tolylguanidine Nitrate.*—Prepared similarly from *o*-toluidine hydrochloride, this *salt* had m. p. 131—132° (Found: C, 45·4; H, 5·7. $C_8H_{11}N_3,HNO_3$ requires C, 45·3; H, 5·7%). Höchster Farbwerke, D.R.-P. 172,979, record m. p. 133° for the nitrate but give no preparation or analysis.

m-*Tolylguanidine Sulphate.*—Prepared by the method of Braun (*J. Amer. Chem. Soc.*, 1933, **55**, 1282) from *m*-toluidine and *S*-methyl*iso*thiourea sulphate, this salt melted when pure at 220—221°. Braun gives m. p. 215—217° (Found: C, 48·5; H, 6·0. Calc.: C, 48·5; H, 6·1%).

as.-o-*Xylylguanidine Nitrate.*—From *o*-xylidine hydrochloride (3·9 g.), this *salt* was obtained as needles, yield 4·8 g. Recrystallised from 6 parts of boiling water it separated in prisms, m. p. 184—185° (Found: C, 48·2; H, 6·2; N, 24·8. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2; N, 24·8%).

as.-m-*Xylylguanidine nitrate* prepared similarly is soluble in 4 parts of boiling water and separates in small clusters of plates, m. p. 174—175° (Found: C, 47·9; H, 6·9. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2%).

p-*Xylylguanidine nitrate* prepared in the same way crystallised from water in clusters of tiny prisms, m. p. 161—162° (Found: C, 47·9; H, 6·0. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2%).

p-*Ethylphenylguanidine nitrate* prepared similarly had m. p. 124—125° and crystallised in needles (Found: C, 47·7; H, 6·2. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2%).

p-*Acetophenylguanidine Hydrochloride and Nitrate.*—*p*-Aminoacetophenone hydrochloride (5·7 g.) was boiled with cyanamide (2·8 g., 2 mols.) in alcohol (20 c.c.) for 6 hours and the solution concentrated to a small volume. After keeping at 0° the required *hydrochloride* (2·8 g.) was collected, and on crystallisation from boiling absolute alcohol separated in large rhombs, m. p. 211° (Found: C, 50·7; H, 5·9; N, 19·3. $C_9H_{11}ON_3,HCl$ requires C, 50·6; H, 5·7; N, 19·7%). The mother liquors were combined and the solvent was replaced by water; on adding ammonium nitrate, the required *nitrate* separated as a crystalline meal, yield 1·0 g. It required 5·5 parts of boiling water for solution and separated in bold rough prisms with a yellow tinge, m. p. 242° (decomp.) (Found: C, 45·3; H, 5·1. $C_9H_{11}ON_3,HNO_3$ requires C, 45·0; H, 5·0%).

o-*Anisylguanidine nitrate* prepared from anisidine hydrochloride and cyanamide in the usual way was soluble in 4 parts of boiling water and separated in rugged tablets, m. p. 159—160° (Found: C, 42·0; H, 5·3; N, 24·5. $C_9H_{11}ON_3,HNO_3$ requires C, 42·1; H, 5·3; N, 24·6%).

p-*Anisylguanidine nitrate* prepared similarly separated from water in tablets, m. p. 218° (Found: C, 42·2; H, 5·0; N, 25·0. $C_9H_{11}ON_3,HNO_3$ requires C, 42·0; H, 5·3; N, 24·6%).

p-*Anisylguanidine Hydriodide.*—*p*-Anisyl-*S*-methyl*iso*thiourea hydriodide (3·24 g.) in alcohol (25 c.c.) was treated with aqueous ammonia (20 c.c., *d* 0·88) and boiled for 5 hours. The solution was evaporated to dryness and the residue taken up in ethyl alcohol. The *hydriodide* (1·58 g.) separated in clusters of tablets but on recrystallisation from alcohol formed short prisms, m. p. 179—180° (Found: C, 33·4; H, 4·2; N, 14·1. $C_9H_{11}ON_3,HI$ requires C, 32·8; H, 4·1; N, 14·3%).

p-*Phenetylguanidine nitrate*, prepared from *p*-phenetidine hydrochloride and cyanamide in quantitative yield, crystallised from 3 parts of boiling water in woolly needles, m. p. 171—172° (Found: C, 44·8; H, 5·5. $C_9H_{13}ON_3,HNO_3$ requires C, 44·6; H, 5·8%).

3 : 4-*Dimethoxyphenylguanidine hydrochloride* separated from the usual reaction mixture in needles, which were soluble in 8 parts of boiling alcohol and on recrystallisation had m. p. 225° (Found: C, 46·5; H, 6·1; N, 18·2. $C_9H_{13}O_2N_3,HCl$ requires C, 46·6; H, 6·1; N, 18·2%).

3-*Chloro*-4-*methoxyphenylguanidine hydrochloride* prepared in the usual way was soluble in 12 parts of boiling alcohol and separated in tablets, m. p. 216—217° (Found: C, 40·6; H, 4·5. $C_9H_{10}ON_3Cl$ requires C, 40·7; H, 4·7%).

3 : 4-*Methylenedioxyphenylguanidine hydrochloride* separated from the reaction mixture in excellent yield. It was recrystallised from 5 parts of boiling alcohol and separated in clusters of flattened needles, m. p. 182° (Found: C, 44·8; H, 4·7; N, 19·4. $C_9H_9O_2N_3,HCl$ requires C, 44·5; H, 4·7; N, 19·5%).

Benzylguanidine nitrate was prepared from benzylamine hydrobromide and cyanamide in the usual way, yield 62%. It crystallised from double its volume of boiling water as a mat of needles, m. p. 149—150°. Davis and Elderfield (*J. Amer. Chem. Soc.*, 1932, **54**, 1502) give m. p. 165°. A repetition of the preparation confirmed the lower m. p. (Found: C, 45·5; H, 5·6; N, 26·8. Calc.: C, 45·3; H, 5·7; N, 26·4%). The picrate had m. p. 190—191°, whereas Davis and Elderfield give m. p. 185·5°.

cyclo*Hexylguanidine Hydrochloride.*—Braun's process (*J. Amer. Chem. Soc.*, 1933, **55**, 1281) for the preparation of this salt was not found satisfactory. If the ethyl alcohol as solvent was replaced by butyl alcohol and the solution boiled for six hours a very good yield of the guanidine hydrochloride, m. p. 227°, was obtained.

n-*Butylguanidine Sulphate.*—This *salt* was prepared from butylamine and methyl*iso*thiourea sulphate in boiling 50% aqueous-alcoholic solution. It could be crystallised from 1·4 parts of boiling water and separated as needles, m. p. 215—216°. Davis and Elderfield (*loc. cit.*) give m. p. 206° when crystallised from methyl alcohol–butyl alcohol [Found: C, 36·7; H, 8·5; N, 25·3. $(C_5H_{13}N_3)_2,H_2SO_4$ requires C, 36·6; H, 8·6; N, 25·6%].

Alkylated Guanidines.

N-p-*Tolyl*-N-*methylguanidine Nitrate.*—*N*-Methyl-*p*-toluidine hydrochloride (2·8 g.) and cyanamide (1·4 g., 2 mols.) were boiled in alcohol (20 c.c.) for 5 hours, and a further equal quantity of cyanamide was added and the boiling continued for another 5 hours. The *nitrate* (2·3 g.) obtained in the usual way was recrystallised from 4 volumes of water and separated in clusters of prisms, m. p. 164—165° (Found: C, 47·9; H, 6·2; N, 25·1. $C_9H_{13}N_3,HNO_3$ requires C, 47·8; H, 6·2; N, 24·8%).

N-p-*Tolyl*-N′-*methylguanidine Hydrochloride.*—*p*-Tolylcyanamide (6·6 g.) and methylamine hydrochloride (3·7 g.) in

butyl alcohol (50 c.c.) were boiled for 12 hours. The solvent was removed, and the residue dissolved in water and extracted to remove unused *p*-tolylcyanamide (0·3 g.). The aqueous solution was then evaporated to dryness and the crystalline residue crystallised from absolute ethyl alcohol by careful addition of dry ether, yield 7·5 g. N-p-*tolyl*-N′-*methylguanidine hydrochloride* crystallises in hygroscopic leaflets, m. p. 145° (Found : C, 53·9; H, 6·9; N, 21·2. $C_9H_{13}N_3$,HCl requires C, 54·1; H, 7·1; N, 21·2%). The *picrate* requires 46 parts of boiling alcohol for solution and separates in compact balls of needles, m. p. 207—208° (Found : C, 45·9; H, 4·2. $C_9H_{13}N_3$,$C_6H_3O_7N_3$ requires C, 45·9; H, 4·1%).

N-p-*Tolyl*-N′N′-*dimethylguanidine Hydriodide*.—Tolylcyanamide (6·6 g.) and dimethylamine hydrochloride (4·1 g.) were boiled in *n*-butyl alcohol solution for 12 hours. The solvent was replaced by water, and the aqueous solution ether extracted and then treated with excess of solid sodium iodide. The crystalline precipitate was collected and crystallised from absolute alcohol and ether (yield 9·5 g.) from which the *salt* separated in prisms, m. p. 161—162° (Found : C, 39·5; H, 5·3; N, 13·7. $C_{10}H_{16}N_3$,HI requires C, 39·3; H, 5·3; N, 13·8%). The hydriodide (18·7 g.) was converted into the hydrochloride which crystallised from very concentrated aqueous solution at 0° in prisms as a *monohydrate*, m. p. 76—78°, yield 6·6 g. (Found : C, 52·4; H, 7·9; N, 17·7; H_2O, 5·9. $C_{10}H_{15}N_3$,HCl,H_2O requires C, 51·8; H, 7·8; N, 18·1; H_2O, 7·8%).

N-p-*Tolyl*-N′-*ethylguanidine Hydrochloride*.—This *salt* was prepared in the same way as the methyl compound in good yield. It is best recrystallised by solution in 0·6 parts of hot ethyl alcohol and addition of 1·4 parts of hot ethyl acetate, and separates in clusters of thin plates, m. p. 151° (Found : C, 55·7; H, 7·6; N, 19·9. $C_{10}H_{15}N_3$,HCl requires C, 56·2; H, 7·6; N, 19·7%).

N-p-*Tolyl*-N′-n-*butylguanidine Hydrochloride*.—Prepared in the same way this *salt* was recrystallised by moistening with absolute ethyl alcohol and adding excess of hot ethyl acetate to the clear solution. It crystallised in pearly leaflets, m. p. 114—115° (Found : C, 59·6; H, 8·4; N, 16·8. $C_{12}H_{19}N_3$,HCl requires C, 59·6; H, 8·3; N, 17·4%).

N-p-*Tolyl*-N′N′-*diethylguanidine Hydriodide*.—A solution of the hydrochloride prepared in the same way as the preceding could not be induced to crystallise. It was precipitated as the hydriodide with excess of potassium iodide and separated from 2 volumes of water as a *dihydrate*, m. p. 60° (Found : C, 39·5; H, 6·6; N, 11·1. $C_{12}H_{19}N_3$,HI,$2H_2O$ requires C, 39·0; H, 6·6; N, 11·4%).

N-p-*Tolyl*-N-*ethylguanidine Nitrate*.—*N*-Ethyl-*p*-toluidine hydrochloride (4·2 g.) and cyanamide (2·1 g.) were boiled in ethyl alcohol (20 c.c.) for 5 hours. The *nitrate* (4·0 g.) prepared in the usual way separated from water as pearly scales, m. p. 184° (Found : C, 49·7; H, 6·8. $C_{10}H_{15}N_3$,HNO_3 requires C, 50·0; H, 6·7%).

N-p-*Anisyl*-N-*methylguanidine Hydrochloride*.—*N*-Methyl-*p*-anisidine hydrochloride (4·3 g.) and cyanamide (2·1 g.) in alcohol (20 c.c.) were boiled for 6 hours. On concentration the solution deposited the required *hydrochloride* (3·75 g.) which was soluble in 4 parts of alcohol and separated in stout prisms, m. p. 233° (Found : C, 50·5; H, 6·8. $C_9H_{12}ON_3$,HCl requires C, 50·1; H, 6·5%).

N-p-*Anisyl*-N-*ethylguanidine Hydrochloride*.—This *salt* was prepared in a similar way from *N*-ethyl-*p*-anisidine hydrochloride. It separated from alcohol in elongated tablets, m. p. 231—232° (Found : C, 52·6; H, 7·2. $C_{10}H_{15}ON_3$,HCl requires C, 52·3; H, 7·0%).

N-p-*Anisyl*-N′-*methylguanidine Hydrochloride*.—*p*-Anisylcyanamide (5·0 g.) and methylamine hydrochloride (2·9 g.) were boiled in butyl alcohol (50 c.c.) for 12 hours. The solvent was replaced by water and ether soluble material (0·5 g.) removed. On concentration of the aqueous liquor to a small volume the *hydrochloride* crystallised. It was collected and recrystallised from absolute alcohol by addition of ether and separated in scales, yield 6·9 g., m. p. 165° (Found : C, 50·2; H, 6·6; N, 19·4. $C_9H_{13}ON_3$,HCl requires C, 50·1; H, 6·5; N, 19·5%).

N-p-*Anisyl*-N′-*ethylguanidine Hydrochloride*.—This salt was prepared in a similar way, yield 6·1 g. It was recrystallised by solution in 0·75 part of warm ethyl alcohol and addition of a larger volume of warm ethyl acetate; it separated in short rods, m. p. 167° (Found : C, 52·2; H, 6·5; N, 18·3. $C_{10}H_{15}ON_3$,HCl requires C, 52·3; H, 7·0; N, 18·3%).

N-p-*Anisyl*-N′N′-*diethylguanidine Hydriodide*.—A solution of the hydrochloride was prepared as in the preceeding example but the salt could not be crystallised. It was converted by addition of excess of solid potassium iodide into the crystalline *hydriodide monohydrate*; this could be recrystallised from two volumes of water and separated in stout prisms, m. p. 66° (Found : C, 39·4; H, 6·5; N, 11·2. $C_{12}H_{19}ON_3$,HI,H_2O requires C, 39·2; H, 6·0; N, 11·4%).

N-p-*Anisyl*-N′-*butylguanidine Hydrochloride*.—This *salt* was prepared in a similar way to the *N*′-methyl derivative described above. The product was best crystallised by solution in its own volume of warm alcohol and addition of excess of ethyl acetate, and then separated in clear rhombs, m. p. 124—125° (Found : C, 55·9; H, 7·7. $C_{12}H_{19}ON_3$,HCl requires C, 55·9; H, 7·8%). The *picrate* separates from alcohol in which it is very readily soluble in clusters of plates, m. p. 127—128° (Found : C, 47·9; H, 4·8. $C_{12}H_{19}ON_3$,$C_6H_3O_7N_3$ requires C, 48·0; H, 4·9%).

When the original reaction was carried out in ethyl alcohol instead of butyl alcohol, the ethereal extract of the aqueous solution of the reaction products gave a crystalline substance on evaporation which on crystallisation from absolute alcohol separated in bold diamond-shaped plates, m. p. 218°. This substance is probably 1 : 3 : 5-*trianisyliso*melamine produced by polymerisation of *p*-anisylcyanamide (Found : C, 64·8; H, 5·4. $C_{24}H_{24}O_3N_6$ requires C, 64·8; H, 5·5%).

N-p-*Anisyl*-N′N′-*dimethylguanidine Hydriodide*.—A solution of the hydrochloride was prepared in the usual way but could not be induced to crystallise directly. It was converted into the *hydriodide* by addition of sodium iodide. This very soluble salt separated from its own volume of water in clusters of prisms, m. p. 169—170° (Found : C, 37·7; H, 5·2; N, 12·9. $C_{10}H_{15}ON_3$,HI requires C, 37·4; H, 5·0; N, 13·1%). The *hydrochloride* separated from absolute alcohol on addition of dry ether as a crystalline crust, m. p. 184—185° (Found : C, 51·7; H, 7·2; N, 18·2. $C_{10}H_{15}ON_3$,HCl requires C, 52·3; H, 7·0; N, 18·3%).

N-p-*Anisyl*-N′-iso*propylguanidine Hydriodide*.—*p*-Anisylcyanamide (10·1 g.) and carefully dried *iso*propylamine hydrochloride (9·5 g.) were boiled in butyl alcohol (100 c.c.) for 16 hours. The solvent was removed, water added, and ether soluble material (0·6 g.) removed. The solution was concentrated to about 25 c.c. and excess of potassium iodide added with stirring. The *hydriodide* separated as an oil which eventually solidified, yield 17·53 g. It crystallised from its own volume of ethyl acetate in pointed plates, m. p. 125—126° (Found : C, 39·6; H, 5·6; N, 12·3. $C_{11}H_{17}ON_3$,HI requires C, 39·4; H, 5·4; N, 12·5%).

N-p-*Anisyl*-N′N″-*dimethylguanidine Hydrochloride*.—(*a*) At 100°. Two sealed tubes each containing *N*-*p*-anisyl-*N*′*S*-dimethyl *iso*thiourea hydriodide (6·76 g.) and alcoholic methylamine (20 c.c. of 33%) were heated at 100° for 16 hours. The combined solution containing long white needles was evaporated to dryness, water added, and the crystalline solid (2·4 g.) collected. On crystallisation from water (10 c.c.) this substance separated in long white prisms, m. p. 350°, which proved to be *s*-trimethylguanidine hydriodide (Found : C, 21·4; H, 5·5. Calc. for $C_4H_{11}N_3$,HI: C, 21·0; H, 5·3%). Schenck (*Z. physiol. Chem.*, 1912, **77**, 366) described this salt as needles, unmelted at 290°. Its identity was confirmed by conversion into the picrate, needles, m. p. 215—216° (Found : N, 25·5. Calc. for $C_4H_{11}N_3$,$C_6H_3O_7N_3$: N, 25·5%). Schenck and Kirchhof (*ibid.*, 1926, **153**, 162) give m. p. 216°. The *hydrochloride monohydrate* separates from alcohol in which it is readily soluble in fine needles, which show partial melting below 100° when air-dried, but when dried at 100° have m. p. 260—262° (Found : C, 30·9; H, 9·2. $C_4H_{11}N_3$,HCl,H_2O requires C, 30·9; H, 9·1%).

The aqueous mother liquor on extraction with ether gave *p*-anisidine (2·1 g.) and on fractional crystallisation of the

solids obtained from the aqueous mother liquor from alcohol there were obtained a further quantity (2·12 g.) of *s*-trimethylguanidine hydriodide and N-p-*anisyl*-N′N″-*dimethylguanidine hydriodide* (2·87 g.) as the more soluble component, crystallising in large tablets, m. p. 168—169° (Found: C, 37·6; H, 5·5; N, 13·2. $C_{10}H_{15}ON_3,HI$ requires C, 37·4; H, 5·0; N, 13·1%).

(*b*) At 80°. Three sealed tubes each containing the quantities of starting material as described above were heated at 80° for 8 hours. On fractionation the same substances were isolated as above but in different proportions, thus: *p*-anisidine (0·75 g.), *s*-trimethylguanidine hydriodide (2·0 g.), and *N*-p-anisyl-*N′N″*-dimethylguanidine (15·2 g.). The last was converted into the *hydrochloride* which was best recrystallised by solution in its own volume of boiling alcohol and adding 3·5 volumes of dry ethyl acetate. It separated in tablets, m. p. 185—186° (Found: C, 52·4; H, 7·0. $C_{10}H_{15}ON_3,HCl$ requires C, 52·3; H, 7·0%).

N-p-*Anisyl*-N′N′N″-*trimethylguanidine Hydriodide*.—Two sealed tubes each containing *N*-*p*-anisyl-*N′S*-dimethyl*iso*thiourea hydriodide (3·38 g.) and alcoholic dimethylamine (10 c.c. of 32%) were heated at 80° for 8 hours. The contents of the two tubes were evaporated to dryness, dissolved in water and extracted with ether which removed *p*-anisidine (0·18 g.). The aqueous mother liquor was again evaporated to dryness with addition of absolute alcohol to facilitate the process, and the solid crystalline residue (7·2 g.) was crystallised from dry ethyl acetate (400 c.c.) by careful addition to the boiling solution of just enough absolute alcohol to effect solution. N-p-*Anisyl*-N′N′N″-*trimethylguanidine hydriodide* separated in long prisms, m. p. 140° (Found: C, 39·5; H, 5·7; N, 12·8. $C_{11}H_{17}ON_3,HI$ requires C, 39·4; H, 5·4; N, 12·5%).

N-p-A*nisyl*-NN′-*dimethylguanidine Hydrochloride*.—Two sealed tubes each containing *N*-*p*-anisyl-*NS*-dimethyl*iso*thiourea hydriodide (6·76 g.) and alcoholic methylamine (20 c.c. of 33%) were heated at 80° for 8 hours. The alcohol was removed and replaced by water, and *N*-methyl-*p*-anisidine (0·3 g.) extracted by ether. The water was again removed; the residue on treatment with alcohol crystallised, but attempts to obtain a pure salt by direct crystallisation from alcohol and ether were not successful. On addition of excess of saturated aqueous sodium picrate solution, the *picrate* (10·0 g.) was obtained. It was crystallised from 3 volumes of boiling alcohol in tablets, m. p. 154° (Found: C, 45·8; H, 4·4. $C_{10}H_{15}ON_3,C_6H_3O_7N_3$ requires C, 45·5; H, 4·3%). It was converted into the *hydrochloride*, a hygroscopic salt which separated from absolute alcohol and dry ether in crystalline form, m. p. 158—159° (Found: C, 51·8; H, 7·2; N, 18·2. $C_{10}H_{15}ON_3,HCl$ requires C, 52·3; H, 7·0; N, 18·3%).

N-p-*Anisyl*-NN′N′-*trimethylguanidine Hydriodide*.—*N*-*p*-anisyl-*NS*-dimethyl*iso*thiourea hydriodide (13·52 g.) and alcoholic dimethylamine (40 c.c. of 33%) were heated at 80° under pressure for 8 hours. The above *hydriodide* (11·4 g.) was readily obtained from aqueous solution and crystallised in plates, m. p. 178—179° (Found: C, 39·7; H, 5·8; N, 12·5. $C_{11}H_{17}ON_3,HI$ requires C, 39·4; H, 5·4; N, 12·5%).

N-p-*Anisyl*-NN′N″-*trimethylguanidine Hydriodide*.—*N*-*p*-Anisyl-*NN′S*-trimethyl*iso*thiourea hydriodide (14·08 g.) and alcoholic methylamine (40 c.c. of 33%) were heated at 80° under pressure for 8 hours. The solution was evaporated to dryness, the residue dissolved in water, and *N*-methyl-*p*-anisidine (1·2 g.) removed by ether extraction. On concentration of the aqueous liquor *s*-trimethylguanidine hydriodide (1·54 g., m. p. 342°) separated. The aqueous liquor was now evaporated to dryness and the residue crystallised from alcohol by addition of dry ether. The required hydriodide (10·06 g.) could now be crystallised as a *monohydrate* from water, m. p. 58—60°. On drying over sulphuric acid it lost water and had m. p. 136—138°. The hydrated forms crystallised in tablets (Found: C, 37·8; H, 5·8; N, 11·9. $C_{11}H_{17}ON_3,HI,H_2O$ requires C, 37·4; H, 5·7; N, 11·9%).

N-p-*Anisyl*-NN′N′N″-*tetramethylguanidine Hydrochloride*.—*N*-*p*-Anisyl-*NN′S*-trimethyl*iso*thiourea hydriodide (14 g.) and alcoholic dimethylamine (40 c.c. of 32%) were heated at 80° for 8 hours. The solvent was removed, the residue dissolved in water and *N*-methyl-*p*-anisidine (1·2 g.) removed by ether extraction. The aqueous solution was treated with excess of saturated sodium picrate solution and the p-*anisyltetramethylguanidine picrate* (10·6 g.) collected. On crystallisation from 3 parts of methyl alcohol it separated in well-formed tablets, m. p. 122° (Found: C, 48·3; H, 5·2; N, 18·4. $C_{13}H_{19}ON_5,C_6H_3O_7N_3$ requires C, 48·0; H, 4·9; N, 18·7%). It was converted into the *hydrochloride* which crystallised from a little absolute alcohol in extremely hygroscopic plates, m. p. 142° (Found: Cl, 13·8; $C_{13}H_{19}ON_5,HCl$ requires Cl, 13·8%).

N-p-*Anisyl*-NN′N′N″-*tetramethylguanidine Methopicrate*.—The preceding hydrochloride was treated with concentrated sodium hydroxide solution and the oily base which separated was taken up in amyl alcohol. The amyl alcoholic solution was shaken with potassium hydroxide pellets, then decanted and treated with excess of methyl iodide under reflux on the water-bath. A crystalline methiodide mixed with potassium iodide readily separated and a further quantity was obtained from the mother liquor on addition of ether. The combined iodides in water were converted into chlorides and the potassium chloride was removed by evaporating to dryness and extracting the organic methochloride with absolute alcohol. Attempts to crystallise this methochloride were unsuccessful, so it was converted into the *methopicrate* which separated from 4 volumes of absolute alcohol in tablets, m. p. 103—104° (Found: C, 48·8; 49·2; H, 5·3; 5·1; N, 17·6, 17·7. $C_{13}H_{22}ON_5,C_6H_3O_7N_3$ requires C, 49·1; H, 5·2; N, 18·1%).

The methochloride regenerated from the methopicrate failed to crystallise. It was dissolved in less than its own weight of water and treated with excess of a hot saturated solution of sodium iodide. An oil separated which soon solidified. The *methiodide* was collected and conveniently crystallised from *iso*propyl alcohol, from which it separated in delicate plates, m. p. 173—174° (Found: C, 42·9; H, 6·2. $C_{13}H_{22}ON_5I$ requires C, 43·0; H, 6·1%).

Intermediates.

N-*Ethyl*-p-*toluidine Hydrochloride*.—The following process avoids intermediate purification through a nitroso-derivative. Form-*p*-toluidide (13·5 g.) and ethyl iodide (15·6 g.) were dissolved in alcohol (20 c.c.) and a solution of potassium hydroxide (5·6 g.) in alcohol (40 c.c.) added. The mixture was boiled for 1 hour, then cooled, and one-half the above quantities of ethyl iodide and alcoholic potash added. The solution was then boiled for a further two hours. The alcohol was removed, water added, and the form-*N*-ethyl-*p*-toluidide extracted with ether. The residue left on removing the ether was hydrolysed with hydrochloric acid (20 c.c. of 16%) by boiling for two hours. On evaporation of the solution to dryness with addition of absolute alcohol at intervals the residue crystallised, yield 11·1 g. N-*Ethyl*-p-*toluidine hydrochloride* crystallises from alcohol in hexagonal plates, m. p. 162° (Found: C, 62·5; H, 8·3. $C_9H_{13}N,HCl$ requires C, 62·9; H, 8·2%).

N-*Methyl*-p-*anisidine Hydrochloride*.—This salt was prepared in 85% yield by the same process as in the preceeding using form-*p*-anisidide and methyl iodide. The *hydrochloride* was crystallised either from methyl ethyl ketone or absolute alcohol and separated in needles, m. p. 119—120° (Found: C, 55·2; H, 7·2. $C_9H_{11}ON,HCl$ requires C, 55·3; H, 7·0%).

N-*Ethyl*-p-*anisidine hydrochloride* was prepared in a similar way; when crystallised from alcohol it separated in tablets, m. p. 153° (Found: C, 57·7; H, 7·6. $C_9H_{13}ON,HCl$ requires C, 57·6; H, 7·5%).

p-*Tolylcyanamide*.—This was obtained by an application of (i) Berger's method (*Monatsh.*, 1884, **5**, 219) or (ii) Pierron's method (*Ann. Chim.*, 1908, **15**, 163).

(i) *p*-Tolylthiourea (33·2 g.) and lead acetate (100 g.) were added to a solution of potassium hydroxide (50 g.) in water (500 c.c.) and the mixture was heated on the boiling water-bath for about 15 minutes. The solution was filtered through

a thin layer of kieselguhr to remove lead sulphide and then made just acid to litmus by adding glacial acetic acid. The precipitate which still contained a colourless lead compound was collected, treated with 2N-ammonia (100 c.c.), filtered, and the filtrate acidified with glacial acetic acid. *p*-Tolylcyanamide, m. p. 68°, separated in 62% yield.

(ii) *p*-Tolylthiourea (33·2 g.) was dissolved in boiling water (500 c.c.) containing potassium hydroxide (50 g.) and a solution of copper sulphate (50 g.) in water (500 c.c.) was added. After boiling for 15 minutes the solution was filtered and acidified with glacial acetic acid. The crude *p*-tolylcyanamide, yield 91%, melted at 63°.

p-*Tolylmethylcyanamide.*—*N*-*p*-Tolyl-*N*-methylthiourea (9·0 g.) was suspended in a solution of potassium hydroxide (12·5 g.) in water (125 c.c.). Lead acetate (25 g.) was added and the mixture was heated on the water-bath for 15 minutes. The solution was filtered and the collected lead sulphide was extracted with boiling alcohol. On removal of the solvent *p*-tolylmethylcyanamide (3·5 g.), m. p. 45°, was obtained (Found: C, 74·4; H, 6·4; N, 19·5. Calc. for $C_9H_{10}N_2$: C, 74·0; H, 6·8; N, 19·2%).

p-*Anisylcyanamide.*—This was prepared in 74% yield by Berger's method using lead acetate as described above for *p*-tolylcyanamide. It crystallised from benzene in plates, m. p. 88° (Found: C, 65·1; H, 5·6. $C_8H_8ON_2$ requires C, 64·8; H, 5·4%). When prepared by Pierron's method the yield was 81%.

N-p-*Anisyl*-N-*methylurea.*—N-p-*Anisyl*-N-*methylthiourea* (9·8 g.) suspended in a solution of potassium hydroxide (12·5 g.) in water (125 c.c.) was treated with lead acetate (25 g.) and the solution heated for 15 minutes on the boiling water-bath. After removal of lead sulphide the aqueous solution was neutralised with glacial acetic acid and concentrated to a small volume. Clusters of striated plates, m. p. 157°, separated which proved on analysis to be *N*-*p*-anisyl-*N*-methylurea (Found: C, 60·2; H, 6·5; N, 15·4. Calc. for $C_9H_{12}O_2N_2$: C, 60·0; H, 6·7; N, 15·5%). Hjort, de Beer, Buck, and Ide (*J. Pharm. Exp. Ther.*, 1935, **55**, 152) give m. p. 157°.

N-p-*Anisyl*-S-*methylisothiourea.*—*p*-Anisylthiourea was prepared in the usual way from *p*-anisidine hydrochloride and ammonium thiocyanate in 80% yield. It melted on recrystallisation from water at 220° and crystallised in jagged plates. The m. ps. given in the literature are much lower. Dyson and George (*J.*, 1924, **125**, 1708) give m. p. 210—211°, Dienske (*Rec. Trav. chim.*, 1931, **50**, 407) gives m. p. 213°, whilst Capps and Dehn (*J Amer. Chem. Soc.*, 1932, **54**, 4304) give m. p. 210°.

For conversion into N-p-*anisyl*-S-*methylisothiourea hydriodide*, the parent thiourea (9·1 g.) was digested gently for 30 minutes in alcohol (9 c.c.) with methyl iodide (4 c.c.). The required hydriodide (15·2 g.) was recrystallised from alcohol (20 c.c.) and separated in diamond-shaped plates, m. p. 164—165° (Found: N, 8·7. $C_9H_{12}ON_2S,HI$ requires N, 8·6%). The free *base* liberated by ammonia separated from alcohol in large rhombs, m. p. 115° (Found: C, 55·3; H, 6·2. $C_9H_{12}ON_2S$ requires C, 55·1; H, 6·2%). The *hydrochloride* crystallises from water in needles, m. p. 165° (Found: C, 46·7; H, 5·6; N, 12·0. $C_9H_{12}ON_2S,HCl$ requires C, 46·4; H, 5·6; N, 12·0%).

N-p-*Anisyl*-NS-*dimethylisothiourea hydriodide* was prepared from *N*-*p*-anisyl-*N*-methylthiourea similarly. Recrystallised from 5 volumes of boiling alcohol it separated in striated tablets, m. p. 197° (Found: C, 35·9; H, 4·5; N, 8·2. $C_{10}H_{14}ON_2S,HI$ requires C, 35·5; H, 4·5; N, 8·3%).

N-p-*Anisyl*-N′-*methylthiourea.*—*p*-Anisidine (25·9 g.) in alcohol (13 c.c.) was treated with methyl *iso*thiocyanate (15·4 g.); on keeping the *thiourea* crystallised out, yield 33·3 g. It was recrystallised from 20 volumes of boiling alcohol from which it separated in prismatic needles, m. p. 169° (Found: C, 55·5; H, 6·4; N, 14·6. $C_9H_{12}ON_2S$ requires C, 55·1; H, 6·2; N, 14·3%). It was converted into N-p-*anisyl*-N′S-*dimethylisothiourea hydriodide* in the usual way. This salt was soluble in 6 parts of boiling alcohol and separated in elongated filmy leaflets, m. p. 179° (Found: C, 35·9; H, 4·2; N, 9·2. $C_{10}H_{14}ON_2S,HI$ requires C, 35·5; H, 4·5; N, 9·6%).

N-p-*Anisyl*-NN′-*dimethylthiourea.*—*N*-Methyl-*p*-anisidine (32·65 g.) and methyl *iso*thiocyanate (17·4 g.) in alcohol (16 c.c.) gave on keeping the *thiourea* (38·0 g.). It was recrystallised from boiling alcohol in which it is readily soluble and separated in long prisms, m. p. 106° (Found: C, 57·5; H, 6·5; N, 12·9. $C_{10}H_{14}ON_2S$ requires C, 57·1; H, 6·7; N, 13·3%). It was converted into N-p-*anisyl*-NN′S-*trimethylisothiourea hydriodide* in the usual way. This is a very soluble salt and to effect crystallisation most of the solvent had to be removed. It could be crystallised from a small volume of alcohol from which it separated in six-sided tablets, m. p. 95—97° (Found: C, 37·4; H, 4·9; N, 8·0. $C_{11}H_{16}ON_2S,HI$ requires C, 37·5; H, 4·9; N, 8·0%).

Action of Cuprous Chloride on N-*Nitroso*-N-*methyl*-p-*anisidine.*—*N*-Methyl-*p*-anisidine hydrochloride (34·9 g.) containing a small proportion of non-methylated base was diazotised in hydrochloric acid solution and added to a solution of cuprous chloride (40 g.) in concentrated hydrochloric acid (286 c.c., *d* 1·16). The solution was heated on the water-bath until there was no further evolution of gas. The copper was removed as sulphide, the solution made alkaline, and the base, which coloured up very rapidly, extracted by ether and fractionally distilled, giving 13·4 g., b. p. 135—136°/19 mm. It was converted into the hydrochloride and fractionated from methyl ethyl ketone; *N*-methyl-*p*-anisidine hydrochloride (6·7 g., m. p. 118°) was the least soluble fraction, and from the mother liquor 2-*chloro*-4-*methoxy*-N-*methylaniline hydrochloride* (1·3 g.) was obtained. It crystallised from methyl ethyl ketone in octahedra, m. p. 156° (Found: C, 46·3; H, 5·2. $C_8H_{10}ONCl,HCl$ requires C, 46·2; H, 5·3%). The *picrate* separated from alcohol in clusters of slender prisms, m. p. 125° (Found: C, 42·4; H, 3·5; N, 13·9. $C_8H_{10}ONCl,C_6H_3O_7N_3$ requires C, 41·9; H, 3·3; N, 14·0%).

2-*Chloro*-4-*nitroanisole.*—Smooth nitration of 2-chloroanisole proved difficult. Reverdin and Eckland (*Ber.*, 1899, **32**, 2622) obtained this chloronitroanisole in unstated yield by adding one part of nitric acid (*d* 1·4) to chloroanisole. An experiment on these lines gave less than a 10% yield of required nitro-compound. After many trials the following two-stage process was adopted. Chloroanisole (7·1 g.) and acetic anhydride (7 c.c.) were heated with stirring to 80° and nitric acid (5·1 c.c., *d* 1·4) was added dropwise. When all had been added, the flask was heated in the boiling water-bath for 2·5 hours and then diluted with water. The semi-solid mass was separated and pressed to free it from oil; yield of crude 2-chloro-4-nitroanisole, m. p. 94°, 46%. The oil from a series of batches was recovered and dried and re-nitrated under similar conditions; most of it then became converted into the required chloronitroanisole. One crystallisation from methyl alcohol gave the pure material.

3-*Chloro*-4-*methoxyformanilide.*—The foregoing nitro-compound was reduced with tin and hydrochloric acid in presence of alcohol and the base obtained in excellent yield, m. p. 62° in agreement with Reverdin and Eckhard (*loc. cit.*). It gave a *hydrochloride*, pearly scales from alcohol, m. p. 278—279° (Found: C, 43·5; H, 4·7. C_7H_8ONCl,HCl requires C, 43·3; H, 4·7%).

3-Chloro-4-methoxyaniline (5·5 g.) and formic acid (5 c.c., 98%) were boiled for 3 hours and the 3-chloro-4-methoxyformanilide (5·2 g.) was isolated by appropriate ether extraction. It separated from 3 parts of benzene in clusters of needles, m. p. 84° (Found: C, 52·0; H, 4·6; N, 8·0. $C_8H_8O_2NCl$ requires C, 51·8; H, 4·3; N, 7·6%).

3-*Chloro*-4-*methoxy*-N-*methylformanilide.*—3-Chloro-4-methoxyformanilide (4·63 g.) and methyl iodide (3·55 g.) in alcohol (25 c.c.) were heated with a solution of potassium hydroxide (1·4 g.) in alcohol (10 c.c.) and the resulting solution was boiled for 1 hour. The solution was cooled and one-half the above quantities of methyl iodide and alcoholic potash added; the solution was then boiled for a further 1 hour. The solvent was removed, water added, and the product isolated by ether extraction. 3-*Chloro*-4-*methoxy*-N-*methylformanilide* (3·6 g.) crystallised from alcohol in diamond-shaped plates, m. p. 72—73° (Found: C, 54·4; H, 5·4; N, 6·8. $C_9H_{10}O_2NCl$ requires C, 54·1; H, 5·1; N, 7·0%). On hydrolysis with boiling 16% hydrochloric acid it gave 3-*chloro*-4-*methoxy*-N-*methylaniline hydrochloride* as columns or tablets from absolute alcohol, m. p. 189° (Found: C, 46·0; H, 5·3; N, 6·8. $C_8H_{10}ONCl,HCl$

requires C, 46·1; H, 5·3; N, 6·7%). The *picrate*, fine needles from water, had m. p. 97°, but when dried at 95° it had m. p. 141—143° (Found: loss at 100°, 3·4. $C_8H_{10}ONCl,C_6H_3O_7N_3,H_2O$ requires H_2O, 4·3%. On dried salt: C, 41·9; H, 3·3. $C_9H_{10}ONCl,C_6H_3O_7N_3$ requires C, 41·9; H, 3·3%). Both these salts were quite different from the two parallel salts from the chloro-*N*-methyl-*p*-anisidine described above.

Reduction of p-*Nitroanisole with Tin and Hydrochloric Acid.*—*p*-Nitroanisole (20 g.), tin foil (40 g.), and concentrated hydrochloric acid (100 c.c.) were allowed to react as violently as possible (Hurst and Thorpe, *J.*, 1915, **107**, 938). The reaction is over in one or two minutes but is very slow if granulated tin is used. The total base produced was recovered as hydrochloride, yield 19·3 g. It was dissolved in water (100 c.c.) and fractionally basified by addition of 13 portions, each of 6 c.c., of 2N-sodium hydroxide. Each fraction was extracted once with chloroform (10 c.c.). On removing the chloroform from each fraction the residues, with the exception of the first, readily crystallised and all except the first two had the m. p. of *p*-anisidine. Only the first two gave the copper-wire test for presence of halogen. The second fraction on acetylation proved to be mainly *p*-anisidine, but the first fraction (1·0 g.) on acetylation solidified and gave 2-chloro-4-methoxyacetanilide, 0·53 g. from benzene, m. p. 110—111° (Found: C, 54·4; H, 5·4; N, 6·8. Calc. for $C_9H_{10}O_2NCl$: C, 54·1; H, 5·1; N, 7·0%), and the benzene mother liquor on addition of petrol gave acet-*p*-anisidide, 80 mg.

Diguanides.

For the preparation of the diguanides from anilines, the hydrochloride of the aniline and the dicyanodiamide were boiled together in aqueous solution for 6 hours, the diguanide often separating from the solution when cold. The following new diguanides were prepared in good yield in this way. m-*Chlorophenyldiguanide hydrochloride*, m. p. 197—198°, fine needles from water (Found: C, 38·8; H, 4·4; N, 28·0. $C_8H_{10}N_5Cl,HCl$ requires C, 38·7; H, 4·5; N, 28·2%). p-*Chlorophenyldiguanide hydrochloride*, m. p. 255°, plates from water (Found: C, 39·1; H, 4·2; N, 27·8. $C_8H_{10}N_5Cl,HCl$ requires C, 38·7; H, 4·5; N, 28·2%). Strukov, Sychra, and Smirnov (*J. Chem. Ind. U.S.S.R.*, 1941, **18**, 22) have described this salt as having m. p. 226°. p-*Bromophenyldiguanide hydrochloride*, m. p. 259°, plates from water (Found: C, 33·4; H, 3·9. $C_8H_{10}N_5Br$, HCl requires C, 32·8; H, 3·8%). o-*Tolyldiguanide hydrochloride*, m. p. 242—243°, stout prisms from water (Found: C, 47·8; H, 6·2; N, 30·6. $C_9H_{13}N_5,HCl$ requires C, 47·5; H, 6·2; N, 30·8%). Beutel (*Annalen*, 1900, **310**, 337) describes a hemihydrate which loses water in the air and has m. p. 229°. m-*Tolyldiguanide hydrochloride*, m. p. 225—226°, rods from water (Found: C, 47·8; H, 6·2. $C_9H_{13}N_5,HCl$ requires C, 47·5; H, 6·2%). Beutel (*loc. cit.*) describes a hemihydrate which readily loses water in the air and has m. p. 211°; he attributes a similar degree of hydration to *p*-tolyldiguanide hydrochloride, for which he gives m. p. 235° (anhydrous). Braun (*J. Amer. Chem. Soc.*, 1933, **55**, 1282) finds the *p*-tolyl salt to be anhydrous with m. p. 245—247°, and this agrees with our own finding. 3 : 4-*Xylyldiguanide hydrochloride*, m. p. 225—226°, needles from water (Found: C, 50·2; H, 6·4; N, 28·7. $C_{10}H_{15}N_5,HCl$ requires C, 49·7; H, 6·7; N, 29·0%). 2 : 4-*Xylyldiguanide hydrochloride*, m. p. 256°, flat needles from water (Found: C, 50·1; H, 6·8; N, 28·7. $C_{10}H_{16}N_5,HCl$ requires C, 49·7; N, 28·7; N, 28·7%). 2 : 5-*Xylyldiguanide hydrochloride*, m. p. 219—220°, tablets from water (Found: C, 50·0; H, 6·7; N, 28·7. $C_{10}H_{15}N_5HCl$ requires C, 49·7; H, 6·7; N, 29·0%). p-*Ethylphenyldiguanide hydrochloride*, m. p. 225—226°, clusters of needles from water (Found: C, 49·8; H, 6·4. $C_{10}H_{15}N_5,HCl$ requires C, 49·7; H, 6·7%). p-*Acetophenonediguanide hydrochloride*, m. p. 222°, needles from water (Found: C, 47·4; H, 5·3. $C_{10}H_{13}ON_5,HCl$ requires C, 47·0; H, 5·5%). o-*Anisyldiguanide hydrochloride monohydrate*, m. p. 216—217°, short stout prisms from water (Found: C, 41·9; H, 5·7; N, 26·6; H_2O, 5·7. $C_9H_{13}ON_5,HCl$ requires C, 41·3; H, 6·2; N, 26·8; H_2O, 6·9%). 3 : 4-*Methylenedioxyphenyldiguanide hydrochloride*, m. p. 237—238°, square plates from water (Found: C, 42·3; H, 4·6; $C_9H_{11}O_2N_5,HCl$ requires C, 41·9; H, 4·7%). N-p-*Tolyl*-N-*methyldiguanide hydrochloride*, m. p. 231°, clusters of pointed tablets from water (Found: C, 50·1; H, 6·8; N, 29·3. $C_{10}H_{15}N_5,HCl$ requires C, 49·7; H, 6·7; N, 29·0%). N-p-*Tolyl*-N-*ethyldiguanide hydrochloride*, m. p. 186—187° from alcohol on addition of ethyl acetate, clusters of tiny needles which change on keeping in contact with the saturated solution into plates (Found: C, 51·6; H, 7·3; N, 27·0. $C_{11}H_{17}N_5,HCl$ requires C, 51·6; H, 7·1; N, 27·4%). N-p-*Anisyl*-N-*methyldiguanide hydrochloride dihydrate*, m. p. 203°, needles from water (Found: C, 41·1; H, 6·9; H_2O, 12·4. $C_{10}H_{16}ON_5,HCl,2H_2O$ requires C, 40·9; H, 6·8; H_2O, 12·3%). N-p-*Anisyl*-N-*ethyldiguanide hydrochloride*, m. p. 189°, stout crystals from alcohol (Found: C, 49·0; H, 7·0. $C_{11}H_{17}ON_5,HCl$ requires C, 48·6; H, 6·7%).

p-Anisyldiguanide hydrochloride was obtained by Lumière and Perrin (*Bull. Soc. chim.*, 1905, **33**, 206) by melting together *p*-anisidine hydrochloride and dicyanodiamide with m. p. 221—222°. When prepared in boiling aqueous solution we find m. p. 235—236° (Found: C, 44·7; H, 5·7. Calc. for $C_9H_{13}ON_5,HCl$: C, 44·3; H, 5·8%).

p-Phenetyldiguanide hydrochloride prepared by Lumière and Perrin (*loc. cit.*) by melting together the components is recorded as having m. p. 209—210°. Cohn (*J. pr. Chem.*, 1911, **84**, 400) prepared it in boiling aqueous solution and records m. p. 170—172°. We have repeated Cohn's preparation and find the salt to crystallise in stout plates, m. p. 220° (Found: C, 46·9; H, 6·0; N, 27·7. Calc. for $C_{10}H_{15}ON_5,HCl$: C, 46·6; H, 6·3; N, 27·2%).

We are indebted to Imperial Chemical Industries Ltd. and to May and Baker Ltd. for gifts of chemicals, to Mr. E. V. Wright for skilled technical assistance in the preparation of many of the compounds, and to Miss R. Berson for assistance on the biological side.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
HAMPSTEAD, LONDON, N.W. 3.

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236. *The Chemistry of the Pyrrocolines. Part I. 2-Methyl- and 2-Phenyl-pyrrocoline.*

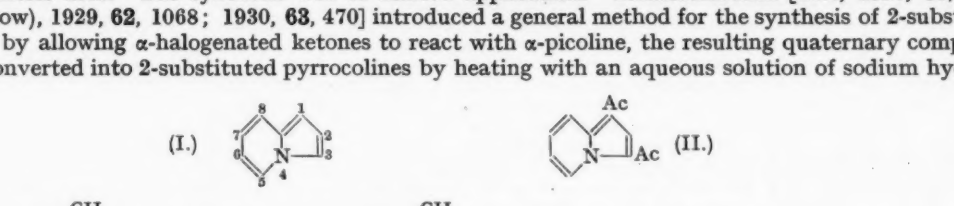
By E. T. BORROWS, D. O. HOLLAND, and J. KENYON.

A number of derivatives of 2-methyl- and 2-phenyl-pyrrocoline has been prepared and studied.

IN view of the increasing interest being shown in the chemistry of heterocyclic compounds, especially those containing nitrogen, it is perhaps surprising that little attention has been paid to the pyrrocoline ring system (I).* Scholtz [*Ber.*, 1912, **45**, 734; *Archiv Pharm.*, 1913, **251**, 666; (with Fraude), *Ber.*, 1912, **45**, 1718;

* Scholtz called this base "pyrrocoline," but later used the name "pyrindole" as suggested by Angeli (*Ber.*, 1890, **23**, 1795, 2154; *Gazzetta*, 1890, **20**, 761). Tschitschibabin and later German and Japanese workers have adopted the name "indolizine," with the following numbering:

1913, **46**, 1069] discovered pyrrocoline during an investigation of the action of acetic anhydride on α-picoline at high temperatures, the initial compound obtained, $C_{12}H_{11}O_2N$ (II), yielding pyrrocoline after hydrolysis with hydrochloric acid. The synthesis was of limited application. Tschitschibabin [*Ber.*, 1927, **60**, 1607; (with Stepanow), 1929, **62**, 1068; 1930, **63**, 470] introduced a general method for the synthesis of 2-substituted pyrrocolines by allowing α-halogenated ketones to react with α-picoline, the resulting quaternary compounds (III) being converted into 2-substituted pyrrocolines by heating with an aqueous solution of sodium hydrogen



carbonate. Diels and his collaborators found that the pyridocoline (quinolizine) derivatives obtained by the action of acetylenedicarboxylic esters on pyridine and similar bases could readily be broken down to compounds of the pyrrocoline series (Diels and Schrum, *Annalen*, 1937, **530**, 68, and earlier papers) and Brand and Reuter (*Ber.*, 1939, **72**, 1669) isolated the parent base in small yield from the product of the reduction of 2-(γγγ-trichloro-β-hydroxypropyl)pyridine with zinc and sulphuric acid. Finally, Wilson (*J.*, 1945, 63) has recently reported pyrrocoline as one of the by-products in the catalytic conversion furan into pyrrole.

The initial product (II) of reaction between α-picoline and acetic anhydride was not thought by Scholtz to possess a pyrrocoline nucleus, but Tschitschibabin showed that it was 1 : 3-diacetylpyrrocoline, and prepared it by the stepwise acetylation of pyrrocoline itself. It is clear that Scholtz failed to assign the correct structure to (II) because ketonic reagents reacted with only one carbonyl group. Tschitschibabin pointed out that this lack of reactivity was not inconsistent with a diacetylpyrrocoline structure, since several α-acetyl-*N*-alkylpyrroles were known which behaved similarly. In support of this he found that neither the monoacetylpyrrocoline prepared by Scholtz nor the monoacetyl derivative of 2-methylpyrrocoline reacted with phenylhydrazine. Further acetylation of these two compounds gave 1 : 3-diacetyl-pyrrocoline and -2-methylpyrrocoline, respectively, both of which gave monophenylhydrazones. Scholtz did not report the failure of his compound to react with phenylhydrazine, but it is noteworthy that he found that the monoacetyl derivative of 7-methylpyrrocoline (from αγ-lutidine and acetic anhydride) readily formed a phenylhydrazone at room temperature.

Working with the readily obtainable 2-methyl- and 2-phenyl-pyrrocolines, we have found that, although their monoacetyl derivatives do not give phenylhydrazones under the usual conditions, yet 2 : 4-*dinitrophenylhydrazones* are readily formed at room temperature. The corresponding diacetyl compounds also give *monodinitrophenylhydrazones*, probably owing to the low solubility of these derivatives.

The 2-methylpyrrocoline used for this work was prepared by the method of Tschitschibabin and Stepanow but in rather lower yield. The reaction between α-picoline and chloroacetone was also carried out on the small scale in a variety of solvents, including carbon tetrachloride, acetone, alcohol, water, and acetic acid, but the yields were not improved. We have confirmed that the m. p. of 2-methylpyrrocoline is 59·5°, as found by Kondo and Osawa (*J. Pharm. Soc. Japan*, 1936, **56**, 73; *Chem. Abs.*, 1938, **32**, 5837), and not 68° as given by Tschitschibabin. The preparation of 2-phenylpyrrocoline, which Tschitschibabin carried out on the small scale, had to be effected in alcoholic solution, as the reaction was strongly exothermic and led to much decomposition when the reactants were used undiluted.

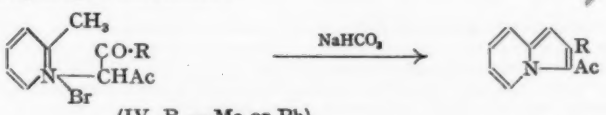
The *monoacetyl* derivative of 2-phenylpyrrocoline, not previously described, was prepared in good yield by Scholtz's method. It is a low-melting solid (m. p. 64°) rapidly hydrolysed to 2-phenylpyrrocoline by mineral acids. Solution in concentrated hydrochloric acid at room temperature, followed by dilution with water, is sufficient to remove the acetyl group, and even heating in 50% aqueous acetic acid causes slow hydrolysis. The 2-methyl analogue is rather more resistant to hydrolysis, complete deacetylation occurring after 2½ minutes' heating at 100° in dilute hydrochloric acid.

Attempts to prepare the acetyl derivative of 2-phenylpyrrocoline by heating with acetyl chloride or bromide were unsuccessful. This lack of reactivity is surprising in view of the ease with which carbonyl chloride and benzoyl chloride react with pyrrocoline itself, and especially so since 2-phenylpyrrocoline also reacts readily with benzoyl chloride to produce a *monobenzoyl* derivative. An unstable hydrochloride, believed to be *2-phenylpyrrocoline hydrochloride*, is also formed during the reaction, but no better yields were obtained when the reaction was carried out in the presence of pyridine. This same benzoyl derivative could also be prepared by fusing the pyrrocoline with benzoic anhydride and sodium benzoate : it did not form a 2 : 4-dinitrophenylhydrazone. Ochiai (*J. Pharm. Soc. Japan*, 1940, **60**, 164; *Chem. Abs.*, 1940, **34**, 5449) has recently reported that acetyl chloride reacts with 2-methylpyrrocoline only with difficulty, even in the presence of a large excess of aluminium chloride, to give a very small yield of 1 : 3-diacetyl-2-methylpyrrocoline. He found, on the other hand, that this compound was readily formed when the monoacetyl derivative of 2-methylpyrrocoline, as prepared by Tschitschibabin, was allowed to react in tetrachloroethane solution under the same conditions. We have repeated this work on the small scale (2 g.) but could only isolate unchanged starting material from the

resulting dark gum. Since this diacetyl compound is readily prepared in fair yield by the action of acetic anhydride on the monoacetyl derivative at high temperature, the reaction with acetyl chloride was not further examined. Improvements in Tschitschibabin's method leading to a better yield (48% compared with 31%) and greater ease of isolation are described in the experimental section. 1 : 3-Diacetyl-2-methylpyrrocoline is somewhat more resistant to hydrolysis than the monoacetyl compound.

The preparation of 1 : 3-*diacetyl-2-phenylpyrrocoline* by heating the monoacetyl compound at high temperatures with acetic anhydride was less successful (13% yield) and the Friedel–Crafts reaction was therefore examined. The required product was obtained in good yield (82%) when the reaction was carried out essentially according to Ochiai's procedure for the 2-methyl analogue. This diacetyl compound is completely hydrolysed to 2-phenylpyrrocoline by heating an acid solution on the steam-bath for 2 minutes. 2-Phenylpyrrocoline itself was also found to react well with acetyl chloride in carbon disulphide solution, provided a large excess (3 mols.) of aluminium chloride were present. There was no reaction when less catalyst (1·5 mols.) was used, even on heating on the steam-bath. Besides unchanged 2-phenylpyrrocoline, and 1 : 3-diacetyl-2-phenylpyrrocoline, a monoacetyl compound, m. p. 240—241°, was also isolated from the reaction mixture. This on oxidation with perhydrol α-picolinic acid *N*-oxide and *p*-acetylbenzoic acid, thus establishing with some certainty that this compound was 2-(p-*acetylphenyl*)*pyrrocoline*. The use of perhydrol to open the pyrrocoline nucleus was first carried out by Diels and Meyer (*Annalen*, **1934**, **513**, 129), and we have found it of value.

Both Scholtz and Tschitschibabin were of the opinion that the acetyl group entered the 3-position of the pyrrocoline nucleus in the monoacetyl derivatives, by analogy with the acetyl derivatives of simple pyrroles. That these groups in both the mono- and the di-acetyl derivatives of 2-methyl- and 2-phenyl-pyrrocoline are in the 5-membered ring appears very probable, since on oxidation with perhydrol α-picolinic acid *N*-oxide is formed (together with benzoic acid in the 2-phenyl derivatives). However, the importance of establishing beyond all reasonable doubt the position of the acetyl group in the monoacetyl compounds became apparent during the course of this work (see following papers) and we had hoped to effect this by the reaction of α-picoline with bromo- or chloro-acetylacetone and bromobenzoylacetone followed by ring closure of the resulting quaternary compounds with sodium hydrogen carbonate :

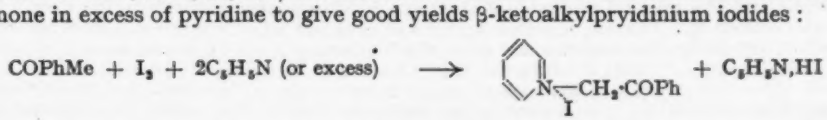


(IV, R = Me or Ph)

From the work of Kröhnke and Timmler (*Ber.*, **1936**, **69**, 614) with dibenzoylmethylpyridinium bromide it was clear that the acetyl group in these quaternary compounds would be very labile. It was expected that some of the required products would be obtained with the very mild alkali used, but with these halogenated diketones only 2-methyl- and 2-phenyl-pyrrocoline, respectively, in small yield could be isolated. The reaction of α-picoline with chloroacetylacetone was studied in some detail, and it would appear from our experiments that the required quaternary salt (as IV, R = Me) is formed in the initial reaction (albeit in very low yield) but that even on warming an aqueous solution in the presence of sodium hydrogen carbonate one acetyl group is lost. In the presence of magnesium oxide and sodium acetate there was no apparent reaction, even on prolonged heating, but in that of piperidine, 2-methylpyrrocoline was obtained even at room temperature. From the weights of the *chloroplatinates* of the quaternary compounds first formed in these reactions, it appeared that ring closure and loss of the acetyl group were practically quantitative. Attempts to prepare the ethyl esters of 2-methyl- and 2-phenyl-pyrrocoline-3-carboxylic acid from α-picoline and α-chloroacetoacetic ester and α-bromobenzoylacetic ester, respectively, in the hope that the required 3-acetyl derivatives might be synthesised in a Claisen condensation, for example, likewise led only to small yields of the parent pyrrocolines. The position of the acetyl group in these compounds was finally established by reduction, and the work carried out in this connection is reported separately (see Part IV).

The recorded preparation by Tschitschibabin of non-crystallisable benzpyrrocolines by the reaction of quinaldine with α-halogenated ketones seemed worthy of further study, and we examined the action of chloroacetone and of phenacyl bromide on this base. From the initial crystalline reaction products only quinaldine hydrochloride and bromide respectively could be isolated, however.

King (*J. Amer. Chem. Soc.*, **1944**, **66**, 894) has described a reaction between iodine and a solution of a ketone such as acetophenone in excess of pyridine to give good yields β-ketoalkylpryidinium iodides :



By using acetone and acetophenone in excess of α-picoline we adapted this reaction to the preparation of 2-methyl- and 2-phenyl-pyrrocoline, but obtained only small yields. The reaction may be useful when the required halogeno-ketone is difficult to prepare, but we have not fully investigated its potentialities.

Experimental.

In all experiments, commercial α-picoline, dried over sodium hydroxide, b. p. 127·5—129·5°/763 mm., was employed. All m. p.'s are uncorrected.

2-*Methylpyrrocoline.*—The method described by Tschitschibabin and Stepanow (*loc. cit.*, 1929) for the preparation of this compound has been somewhat modified. A mixture of α-picoline (180 g.) and chloroacetone (b. p. 118·5—120·5°/760 mm.; Cl, 39·7% ≡ 93% of monochloroacetone) (180 g.) was heated on a steam-bath. After 10—15 mins. a vigorous reaction set in and the mixture was removed from the bath until this had subsided (external cooling was sometimes necessary). After 3 hours' heating the resulting dark brown syrup was cooled, diluted with water (2 l.), and the aqueous solution extracted several times with chloroform to remove dark gummy material. Solid sodium hydrogen carbonate was then added until effervescence had ceased, and the liberated α-picoline was extracted with ether. To the final aqueous solution, sodium hydrogen carbonate (300 g.) was added, and the mixture heated on the steam-bath for 1 hr. The 2-methylpyrrocoline was removed in a current of steam, dissolved in ether, the solution dried (Na_2SO_4), and the solvent removed (125 g., 49%), m. p. 57—59°.

The cream-coloured solid was sufficiently pure for most purposes, but when required completely pure it was sublimed. (We confirm Tschitschibabin's observations that sublimation is much more effective than recrystallisation or distillation in a vacuum.) In a large sublimation apparatus at 12 mm. pressure with a bath temperature rising to 80°, we have purified 50 g. at a time, in approximately 10 hours; m. p. 59·5°, b. p. 100°/12 mm.

N-*Acetonyl-α-picolinium Chloroplatinate* (as III, R = Me).—A portion of the aqueous solution, after removal of tarry by-products in the above preparation, was treated with sodium hydrogen carbonate until effervescence ceased, and the mixture warmed to about 40° to complete the liberation of α-picoline, which was then thoroughly extracted with ether. The brown aqueous layer was made slightly acid with hydrochloric acid and treated with charcoal several times at room temperature until a pale straw-coloured solution resulted. Addition of an acid solution of chloroplatinic acid precipitated the chloroplatinate as a buff-coloured powder, m. p. 205° (decomp.) after drying at 100° [Tschitschibabin, *loc. cit.*, gives m. p. 202° (decomp.)] (Found: C, 29·9; H, 3·6; N, 4·1; Pt, 26·5. Calc.: C, 29·8; H, 3·6; N, 3·9; Pt, 26·9%).

The corresponding *picrate*, similarly prepared, separated after standing in the ice-chest; recrystallised from alcohol, it formed tiny, rectangular, bright yellow platelets, m. p. 146·5—147·5° (shrinking with slight melting from 139°) (Found: C, 47·7; H, 3·7; N, 15·2. $C_{15}H_{14}O_8N_4$ requires C, 47·6; H, 3·7; N, 14·8%).

2-*Methylpyrrocoline Salts.*—*Picrate.* A concentrated solution of picric acid in dry ethyl acetate was added to an ethereal solution of freshly sublimed 2-methylpyrrocoline, and the bright yellow precipitate removed and washed well with ether [m. p. 110—111° (decomp.)]. The *picrate* separates from alcohol or ethyl acetate in greenish-yellow needles, m. p. 111—112° (decomp.) (Found: C, 50·3; H, 3·4; N, 15·4. $C_{15}H_{12}O_7N_4$ requires C, 50·0; H, 3·3; N, 15·5%). Recrystallisation from acetic acid gave greenish-yellow needles, m. p. 102—103° (decomp.), which apparently contain 0·5 mol. of acetic acid (Found: C, 49·5; H, 3·5; N, 14·5. $C_{15}H_{12}O_7N_4,0{\cdot}5C_2H_4O_2$ requires C, 49·2; H, 3·6; N, 14·4%). Attempted recrystallisation from acetone gave a greenish product which could not be completely purified, m. p. 124° (vigorous decomp.).

Perchlorate. 2-Methylpyrrocoline was dissolved in 60% perchloric acid and the colourless solution kept in a vacuum over phosphoric oxide for 3 days. The resulting orange syrup, on being rubbed with dry ethyl acetate, yielded a white solid, m. p. 88—92°, which separated from methyl alcohol–ethyl acetate in white needles, m. p. 92—93·5° (slight melting from 82°) (Found: C, 46·5; H, 4·4; N, 6·1; Cl, 15·6. $C_9H_{10}O_4NCl$ requires C, 46·8; H, 4·3; N, 6·1; Cl, 15·3%). This *perchlorate* darkened on keeping and the odour of 2-methylpyrrocoline became noticeable.

Chloroplatinate. This *salt* separated as a buff-coloured powder on adding an aqueous solution of chloroplatinic acid to a solution of the base in dilute hydrochloric acid; it gradually darkened on heating but did not melt at 360° (Found: C, 32·4; H, 3·1; N, 4·4. $C_{18}H_{20}N_2Cl_6Pt$ requires C, 32·2; H, 3·0; N, 4·2%).

2-*Phenylpyrrocoline.*—The method described by Tschitschibabin (*loc. cit.*) was modified in several respects. Phenacyl bromide (291 g.) was added to a solution of α-picoline (144 c.c.) in dry ethyl alcohol (250 c.c.), and the spontaneous reaction controlled by external cooling. Next day the hard mass was broken up, filtered off, and washed with dry alcohol (100 c.c.); 311 g., m. p. 213° (decomp.). From the filtrate and washings after concentration in a vacuum a further 15 g. of phenacyl-α-picolinium bromide (III, R = Ph) were obtained (yield, 73%). A portion recrystallised from alcohol had m. p. 214° (decomp.) [lit., m. p. 215° (decomp.), yield 60%]. Phenacyl-α-picolinium bromide (100 g.) was dissolved in water (1 l.), sodium hydrogen carbonate (100 g.) added, and the mixture brought to the boil. 2-Phenylpyrrocoline separated as a thick magma of iridescent platelets. After 0·5 hr. the mixture was cooled, the solid removed, and the filtrate again boiled to yield a further quantity of the product. The combined crops were washed well with water and dried at 80°; 64 g. (96%), m. p. 213° (decomp.). This product is sufficiently pure for most purposes but can be recrystallised from alcohol in iridescent platelets, m. p. 214° (decomp.) (lit. 215°). 2-Phenylpyrrocoline is only slightly soluble in most organic solvents, even on heating. It is, however, readily soluble in cold formic acid. It is soluble in concentrated mineral acids and is not precipitated on dilution with water.

N-*Phenacyl-α-picolinium chloroplatinate* was formed by addition of a solution of chloroplatinic acid to a solution of the bromide in dilute hydrochloric acid; it was a buff-coloured powder, m. p. 232° (decomp.) (Found: N, 3·45; Pt, 23·5. $C_{36}H_{34}O_2N_2Cl_6Pt$ requires N, 3·4; Pt, 23·4%).

2-*Phenylpyrrocoline picrate* separates when a hot saturated aqueous solution of picric acid is added to a solution of the base in dilute hydrochloric acid. Recrystallised from ethyl acetate, it forms fine greenish-yellow needles, m. p. 161° (decomp.) (Found: C, 56·8; H, 3·5; N, 12·7. $C_{20}H_{14}O_7N_4$ requires C, 56·9; H, 3·3; N, 13·3%).

Oxidation of 2-*Phenylpyrrocoline.*—A suspension of 2-phenylpyrrocoline (3 g.) in a mixture of acetic acid (20 c.c.) and perhydrol (20 c.c.) was warmed cautiously on the steam-bath, and the solid slowly dissolved to produce a very dark solution. When the vigorous reaction, moderated by external cooling, that commenced at this stage was over, the mixture was heated on the steam-bath for 9 hours, during which further perhydrol (20 c.c.) was added portionwise. The resulting clear yellow solution on concentration in a vacuum yielded a syrup which was triturated with water (15 c.c.). The aqueous extract and the residual undissolved products were extracted with ether (25 c.c.). From the aqueous extract, after concentration in a vacuum, a yellow syrup was obtained which deposited α-picolinic acid *N*-oxide; after recrystallisation from dry methyl alcohol, this had m. p. 161·5°(decomp.), not depressed on admixture with an authentic specimen (m. p. 162°, decomp.). From the ethereal extract benzoic acid was separated with some difficulty.

3-*Acetyl-2-methylpyrrocoline.*—A solution of 2-methylpyrrocoline (21 g.) in acetic anhydride (150 c.c.) containing freshly fused sodium acetate (21 g.) was heated under reflux for 7 hrs. The excess of acetic anhydride was largely removed by distillation in a vacuum, and the remainder destroyed by boiling the black residue with alcohol. Water was added to the mixture to dissolve the sodium acetate, and the dark oil extracted with chloroform. The chloroform extract was washed with 2N-sodium hydroxide, then with water, dried ($CaCl_2$), and the solvent removed; the residue was distilled in a vacuum, and the bulk of the material collected at 179—185°/16 mm.; yield 21 g. (75%). The distillate, a yellowish-green solid, was recrystallised from ligroin (charcoal), forming thick cream-coloured clumps, m. p. 83° (lit. 83°).

Benzylidene derivative. This was prepared by the method used by Scholtz for acetylpyrrocoline (*Ber.*, 1912, **45**, 1718). To a solution of 3-acetyl-2-methylpyrrocoline (1 g.) and benzaldehyde (1·5 c.c.) in alcohol (10 c.c.) was added 2N-sodium hydroxide (2 c.c.). After 2 days, addition of a little water to the orange solution precipitated an oil which

solidified to a mass of orange crystals on rubbing; these recrystallised from alcohol in small stout, orange needles, m. p. 102—104° (Found: C, 82·5; H, 6·4; N, 5·5. $C_{16}H_{15}ON$ requires C, 82·8; H, 5·8; N, 5·4%).

2 : 4-*Dinitrophenylhydrazone.* A concentrated solution of 2 : 4-dinitrophenylhydrazine in a mixture of concentrated sulphuric acid and alcohol was added to an alcoholic solution of 3-acetyl-2-methylpyrrocoline at room temperature. A deep red solution was produced at once, and after a few minutes an almost black crystalline powder began to separate. It recrystallised from ethyl acetate (a large volume is needed to dissolve the solid, but the resulting solution must be concentrated considerably) in tiny, almost jet-black, irregular crystals, m. p. 252° (slight decomp.). The crystals appeared blood-red by transmitted light under the microscope (Found: C, 57·9; H, 4·3; N, 19·9. $C_{17}H_{15}O_4N_5$ requires C, 57·8; H, 4·3; N, 19·8%).

3-*Acetyl-2-phenylpyrrocoline.*—2-Phenylpyrrocoline (20 g.) and fused sodium acetate (20 g.) were heated under reflux for six hours with acetic anhydride (200 c.c.). The reaction mixture was worked up essentially as for the 2-methyl analogue, except that the required product was extracted into ether. The brown oil from the dried ethereal extract was distilled rapidly at 0·05 mm., most of the material collecting between 162° and 174° as a yellow solid (22·2 g.; 91%). Distillation at higher pressures is satisfactory provided it be rapid. Recrystallisation from ligroin (b. p. 60—80°) afforded soft, white, flat prisms tinged with green, m. p. 64·5° (Found: C, 81·8; H, 5·5; N, 5·8. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%). The *product* sublimes at 120—130°/0·006 mm.

Dinitrophenylhydrazone. A crude derivative, m. p. 180—186°, separated slowly on addition of Brady's reagent to a solution of the monoacetyl compound in alcohol; the *compound* separated from glacial acetic acid as a dull red microcrystalline powder, m. p. 220—221° (Found: N, 16·9. $C_{22}H_{17}O_4N_5$ requires N, 16·7%).

1 : 3-*Diacetyl-2-methylpyrrocoline.*—A mixture of the monoacetyl compound (10 g.), acetic anhydride (40 c.c.), and acetic acid (30 c.c.) was heated in a sealed tube at 230—240° for 8 hrs. After cooling, the dark solution was evaporated in an open dish, alcohol being added towards the end to facilitate removal of acetic anhydride. The resulting pitch-like solid was extracted 4 times with ligroin (b. p. 100—120°, 100 c.c.) and the combined extracts cooled in the ice-chest; crude 1 : 3-diacetyl-2-methylpyrrocoline separated as a light brown powder (5·5 g.), m. p. 117—120°. Concentration of the mother-liquors in a vacuum gave a partly solid residue which was treated with a little dry acetone and then ligroin, a further 0·5 g. of the diacetyl compound being obtained (48·4% yield). The solid, purified by recrystallisation from ligroin (b. p. 100—120°) after treatment with charcoal, was obtained as stout cream-coloured needles, m. p. 122—123° (lit. m. p. 123°) (Found: C, 72·3; H, 6·0; N, 6·2. Calc.: C, 72·6; H, 6·1; N, 6·5%). Its phenylhydrazone, pale yellow platelets from alcohol, had m. p. 208—210° (decomp.) [lit., 210° (decomp.)].

The 2 : 4-*dinitrophenylhydrazone* was precipitated immediately on the addition of Brady's reagent (2 mols.) to a solution of the diacetyl compound (1 mol.) in warm alcohol, as a dark purple-brown powder. It recrystallised from pyridine in the same form, m. p. 246° (decomp.) (Found: C, 57·4; H, 4·6; N, 18·4. $C_{19}H_{17}O_8N_5$ requires C, 57·7; H, 4·3; N, 17·7%).

Oxidation of 1 : 3-*Diacetyl-2-methylpyrrocoline.*—A solution of the diacetyl derivative (0·5 g.) and perhydrol (5 c.c.) in acetic acid (10 c.c.) was heated under reflux for 1 hr. The solution turned almost black at first but gradually became colourless. Removal of the solvent left a syrup which on rubbing with methyl alcohol turned to a white powder. Crystallisation of this from methyl alcohol yielded α-picolinic acid *N*-oxide, m. p. 160° (decomp.) alone or mixed with an authentic specimen.

1 : 3-*Diacetyl-2-phenylpyrrocoline.*—(*a*) A solution of 3-acetyl-2-phenylpyrrocoline (6 g.) in acetic anhydride (50 c.c.) was heated in a sealed tube at 230—240° for 8 hrs. The contents of the tube, which were only slightly charred, were concentrated in a vacuum leaving a brown syrup which was heated with a little alcohol to destroy the last traces of acetic anhydride. The final residue, after removal of ethyl acetate and alcohol, was extracted with ligroin (b. p. 60—80°) and a small amount of black residue remained. The small quantity of crystalline solid which separated from the cooled ligroin extract was combined with the black residue and recrystallised from aqueous alcohol (charcoal), yielding fawn crystals, 0·95 g, m. p. 169—170°. Recrystallisation from aqueous alcohol yielded colourless platelets or needles, m. p. 172·5—173° (Found: C, 77·8; H, 5·7; N, 5·4. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·1%). From the final petrol extract most of the monoacetyl compound was recovered unchanged.

(*b*) To a solution of acetyl chloride (10 g.) in tetrachloroethane (450 c.c.), powdered aluminium chloride (48 g.) was added followed by 3-acetyl-2-phenylpyrrocoline (30 g.), and the mixture heated at 60° for 1 hr. After 24 hrs. it was poured into 2N-hydrochloric acid (500 c.c.), and the tetrachloroethane removed in a current of steam. The dark green crystalline residue, which separated on cooling, was washed with water and recrystallised from dilute alcohol (charcoal); colourless platelets, (29·2 g.; 82%), m. p. 172—173° alone or when mixed with the *compound* described in (*a*) (Found: C, 77·7; H, 5·6; N, 4·8%).

2 : 4-*Dinitrophenylhydrazone.* Addition of Brady's reagent (2 mols.) to an alcoholic solution of the diacetyl compound precipitated the 2 : 4-*dinitrophenylhydrazone* immediately in fine red crystals, which, after washing with hot acetone, had m. p. 254° (Found: C, 63·0; H, 4·4; N, 15·4. $C_{24}H_{19}O_8N_5$ requires C, 63·0; H, 4·2; N, 15·3%).

Oxidation of 1 : 3-*Diacetyl-2-phenylpyrrocoline.*—A solution of the diacetyl compound (1 g.) in a mixture of perhydrol (6 c.c.) and acetic acid (6 c.c.) was refluxed for 2 hrs. From the resulting clear yellow solution, benzoic acid and α-picolinic acid *N*-oxide were isolated.

Reaction of 2-Phenylpyrrocoline with Acetyl Chloride in the Presence of Aluminium Chloride.—To finely powdered aluminium chloride (12 g.), covered with a solution of acetyl chloride (4·5 c.c.) in dry carbon disulphide (100 c.c.), 2-phenylpyrrocoline (6 g.) was added, and the mixture heated on the steam-bath for 20 hrs. Hydrogen chloride was evolved during the first 4 or 5 hrs., and the pyrrocoline formed a homogeneous syrup with aluminium chloride. After three days, the solvent was removed in a vacuum, and the residual syrup mixed carefully with an excess of 2N-sodium hydroxide. The light brown solid that separated was filtered off, washed with water, dried (6·2 g.), and extracted several times with boiling benzene. The combined benzene extracts (320 c.c.) on cooling deposited 2-(p-*acetylphenyl*)*pyrrocoline* as a fawn crystalline solid, m. p. 225—230° (decomp.). Recrystallisation from benzene (charcoal) yielded pale green iridescent platelets, m. p. 239—241° (decomp.) (1·6 g.; 19%); and after recrystallisation from chloroform, m. p. 240—241° (decomp.) (Found: C, 81·4; H, 5·7; N, 6·1. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%). The benzene filtrate from the recrystallisation yielded, on evaporation to dryness, crude 2-phenylpyrrocoline (0·48 g.).

The original benzene extract (320 c.c.) after the removal of crude *p*-acetylphenylpyrrocoline was concentrated to 50 c.c. and cooled, 0·26 g. of solid [m.p. 212—216° (decomp.)] being obtained. This was filtered off, the filtrate evaporated to dryness in a vacuum, and the residue extracted with ligroin (b. p. 60—80°), leaving a trace of insoluble material. The ligroin extract, on cooling, deposited 2·2 g. (30%) of crude 1 : 3-diacetyl-2-phenylpyrrocoline. On concentration of the filtrate a further small quantity of this material was obtained, but no 3-acetyl-2-phenylpyrrocoline could be detected. The crude diacetyl compound after recrystallisation from ligroin had m. p. 171°, alone and on admixture with a specimen prepared by acetylation of the monoacetyl compound (Found: N, 5·3%).

2-(p-*Acetylphenyl*)*pyrrocoline* 2 : 4-*Dinitrophenylhydrazone.*—Fine red needles, which did not melt at 340°, were obtained when a hot solution of the acetyl compound in acetic acid was added to a hot solution of 2 : 4-dinitrophenylhydrazine sulphate in the same solvent. This was apparently the *sulphate* of the required derivatives (Found: N, 12·4; S, 8·4.

$C_{22}H_{17}O_4N_5,1{\cdot}5H_2SO_4$ requires N, 12·4; S, 8·5%). On treatment with warm water the solid became dark red and flocculent, m. p. approx. 290° (violet decomp.). The aqueous mother-liquors gave a white precipitate with barium chloride solution.

Oxidation of 2-(p-*Acetylphenyl*)*pyrrocoline.*—The acetyl derivative (1·3 g.) was heated on the steam-bath in a mixture of perhydrol (10 c.c.) and acetic acid (10 c.c.), the initial vigorous reaction being controlled by external cooling. After an hour, the mixture was refluxed for 2 hrs., more perhydrol (10 c.c.) added, and refluxing continued for a further 7 hrs. The final yellow solution was concentrated in a vacuum, and the residual yellow solid dissolved in boiling water (25 c.c.). A trace of insoluble oil was removed by filtration through kieselguhr, and the filtrate on cooling deposited a crystalline solid, m. p. 202—207°; this recrystallised from water (charcoal) in needles, m. p. 208°, alone or when mixed with *p*-acetylbenzoic acid. The semicarbazone, m. p. 268°, likewise did not depress the m. p. of *p*-acetylbenzoic acid semicarbazone. From the aqueous filtrate from the crude *p*-acetylbenzoic acid, α-picolinic acid *N*-oxide was obtained in the usual way.

3-*Benzoyl*-2-*phenylpyrrocoline.*—(*a*) 2-Phenylpyrrocoline (4 g.) was dissolved in warm benzoyl chloride (15 c.c.). After 24 hrs. the deep green solution was decanted from the green crystalline solid (1·2 g.) that had separated, and poured with stirring into ligroin (b. p. 60—80°). The crude *benzoyl* derivative which separated was removed and recrystallised twice from alcohol; pale yellow monoclinic crystals, m. p. 137—138° (2·5 g.; 40%) (Found: C, 85·1; H, 5·2; N, 4·9. $C_{21}H_{15}ON$ requires C, 84·8; H, 5·1; N, 4·7%). The green solid (1·2 g., above) was washed with acetone. It was rather deliquescent and difficult to purify, but was obtained as buff-coloured crystalline nodules, m. p. 109° (decomp.), when recrystallised cautiously from methyl cyanide. A satisfactory analysis for chlorine could not be obtained for this material, but as it was readily hydrolysed by water to give 2-phenylpyrrocoline and chlorine ions (benzoic acid was absent) it probably is 2-*phenylpyrrocoline hydrochloride* (Found: C, 83·1; H, 5·65; N, 6·9; Cl, 5·5. $C_{14}H_{11}N,0{\cdot}25HCl$ requires C, 83·1; H, 5·6; N, 6·9; Cl, 4·4%).

(*b*) A mixture of 2-phenylpyrrocoline (2 g.), benzoic anhydride (20 g.), and sodium benzoate (2 g.) was fused and kept at 140—150° for 2 hours. The cooled black melt was triturated with cold 20% sodium hydroxide solution to destroy the anhydride, and the residual brown solid was filtered off and washed with water. Recrystallisation from alcohol (charcoal) gave 3-benzoyl-2-phenylpyrrocoline (1·55 g.; 50%), m. p. 136—138°, alone or when mixed with the material prepared above (*a*).

The *picrate* separated as a red solid when an alcoholic solution of picric acid was added to a hot concentrated alcoholic solution of the benzoyl compound. Recrystallisation from alcohol yielded rust-coloured platelets, m. p. 121—122° (Found: C, 61·4; H, 3·8; N, 10·7. $C_{21}H_{15}ON,C_6H_3O_7N_3$ requires C, 61·6; H, 3·4; N, 10·6%).

3-Benzoyl-2-phenylpyrrocoline is only slightly soluble in hydrochloric acid, but dissolves slowly on heating. On keeping the resulting solution hot for a few minutes, the solid is completely hydrolysed to 2-phenylpyrrocoline. A dinitrophenylhydrazone could not be prepared.

Reaction of 3-*Chloroacetylacetone with* α-*Picoline.*—3-Chloroacetylacetone was prepared in 68% yield by the action of sulphuryl chloride on acetylacetone at 0°, essentially by the method used by Dey (*J.*, 1915, **107**, 1646) for the preparation of ethyl α-chloroacetoacetate (cf. Combes, *Compt. rend.*, 1890, **111**, 273). Attempts to prepare 3-bromoacetylacetone by the method of Auwers and Auffenberg (*Ber.*, 1917, **50**, 951) led only to a very unstable product.

A solution of α-picoline (9·3 g.) and chloroacetylacetone (13·5 g.) in methyl ethyl ketone (50 c.c.) was heated on the steam-bath for 30 hrs. After cooling, the dark brown solution was decanted, leaving a light brown partly solid gum which, after being washed with methyl ethyl ketone, was dissolved in water (12 c.c.), and the aqueous solution extracted with chloroform. The brown aqueous layer on clarification with charcoal at room temperature yielded a pale yellow solution. (It was established that this clarification process does not remove any quaternary compounds present.) Sodium hydrogen carbonate was added until effervescence ceased, and the liberated α-picoline extracted thoroughly with ether. To a portion (2 c.c.) of the final clarified solution (14 c.c.), acidified with hydrochloric acid, a solution of chloroplatinic acid was added. The resulting orange-buff coloured precipitate was filtered off next day, washed with water, and dried at 100° (0·15 g.), m. p. 215—216° (decomp.). Mixed with acetonyl-α-picolinium chloroplatinate (m. p. 205°, decomp.), it had m. p. 190—198°, and is therefore probably N-*diacetylmethyl*-α-*picolinium chloroplatinate* (as IV, R = Me), although the analysis indicated contamination with α-picoline chloroplatinate (Found: C, 27·9; H, 3·3; N, 4·3; Pt, 28·2. $C_{22}H_{28}O_4N_2PtCl_6$ requires C, 33·4; H, 3·5; N, 3·5; Pt, 24·6%).

To a further portion (10 c.c.) of the clarified solution excess of sodium hydrogen carbonate was added, and the solution heated under reflux for 1 hr., to yield 0·46 g. (5%) of 2-methylpyrrocoline. (The odour of α-picoline was noticed when heating was commenced.)

The remaining 2 c.c. of the original clarified solution were mixed with an alcoholic solution of picric acid, and N-*diacetylmethyl*-α-*picolinium picrate* was deposited on scratching. Recrystallised from alcohol, the picrate formed bright yellow needles, m. p. 133°, when cooled slowly, or very tiny pale yellow needles, m. p. 143—143·5°, when cooled rapidly. The analysis was carried out on the latter form (Found: C, 44·7; H, 3·5; N, 14·6. $C_{17}H_{16}O_9N_4,0{\cdot}5C_6H_3O_7N_3$ requires C, 44·9; H, 3·3; N, 14·4%). Mixed with acetonyl-α-picolinium picrate (m. p. 146·5—147·5°), it had m. p. 120—122°.

In a subsequent preparation, the reactants were heated without solvent in an oil-bath at 140—150° for 1 hr., a slightly better yield of 2-methylpyrrocoline being obtained by this procedure (7%). The reaction mixture was worked up as described above, and the final clarified aqueous solution after cautious treatment with sodium hydrogen carbonate was warmed to 40° to complete the release of α-picoline. The chloroplatinate obtained after this treatment, however, melted at 205° (decomp.). Mixed m. p. with acetonyl-α-picolinium chloroplatinate (m. p. 205°, decomp.), 202° (decomp.). Although there was a slight depression in m. p., the analysis of this chloroplatinate agrees fairly well with that for acetonyl-α-picolinium chloroplatinate (Found: C, 29·9; H, 3·5; N, 4·1; Pt, 27·7. Calc.: C, 29·8; H, 3·6; N, 3·9; Pt, 26·8%). Attempts to prepare a picrate from the remaining aqueous solution were unsuccessful, only tiny quantities of a yellow gum being obtained.

Reaction of 3-*Bromobenzoylacetone with* α-*Picoline.*—3-Bromobenzoylacetone (prepared by the method of Kröhnke and Timmler, *loc. cit.*, from benzoylacetone) (2 g.) was added immediately to a solution of α-picoline (1·25 c.c.) in alcohol (2·5 c.c.). After 24 hrs. the supernatant solution was decanted, the residual dark oil dissolved in water, and the α-picoline extracted with ether. The aqueous solution was clarified with charcoal, and a portion (10 c.c.) of the total (45 c.c.) was acidified with hydrochloric acid and mixed with chloroplatinic acid solution. The precipitated chloroplatinate (0·05 g.), m. p. 217° (decomp.), could not be purified. Mixed with phenacyl-α-picolinium chloroplatinate (m. p. 232°, decomp.) it had m. p. 219° (decomp.), indicating that in this case removal of the acetyl group from the quaternary compound had occurred to some extent at this stage. To another portion (25 c.c.) of the clarified aqueous solution was added sodium hydrogen carbonate (2·5 g.), and the mixture heated to boiling for a few minutes; a black oily solid was deposited from which 2-phenylpyrrocoline (0·05 g.) was isolated.

Reaction of Ethyl α-*Chloroacetoacetate with* α-*Picoline.*—Ethyl α-chloroacetoacetate was prepared by the action of sulphuryl chloride on ethyl acetoacetate (Dey, *loc. cit.*,) in 75% yield. A mixture of ethyl α-chloroacetoacetate (10 c.c.) and α-picoline (10 c.c.) was refluxed gently in an oil-bath for 1·5 hrs. After cooling, the dark reaction mixture was diluted with water and filtered through kieselguhr to remove the considerable quantity of tar. To the brown aqueous filtrate

sodium hydrogen carbonate (2 g.) was added, and the mixture refluxed for 1·5 hrs. A current of steam was then passed through, and 2-methylpyrrocoline (0·9 g.) obtained.

Reaction of Ethyl α-Bromobenzoylacetate with α-Picoline.—Ethyl benzoylacetate was prepared essentially by the method of Dorsch (*J. Amer. Chem. Soc.*, 1932, **54**, 2960), and brominated according to the procedure of McElvain and Hawk (*ibid.*, p. 287). A mixture of ethyl α-bromobenzoylacetate (2·9 g.) and α-picoline (1 g.) was kept at room temperature for 2 days, heated on the steam-bath for 3 hrs., and then kept at room temperature for a further 2 days. The resulting dark brown syrup was shaken with water and ether, the ethereal extract discarded, and the aqueous layer clarified with charcoal. To this yellow solution was added potassium hydrogen carbonate (2 g.), and the solution heated to boiling; 2-phenylpyrrocoline (0·02 g.; 1%) separated. This poor yield could not be impoved although a variety of conditions were tried.

Reaction of Phenacyl Bromide with Quinaldine.—A mixture of phenacyl bromide (6 g.) and quinaldine (4·2 g.) after standing at room temperature for 2 days had set to a crystalline mass. This was freed from contaminating syrup and washed with dry acetone, leaving a pale pink crystalline solid, m. p. 223°. The filtrate and acetone washings after concentration, on being heated on the steam-bath for 1 hr., yielded a further small amount of the same solid. The combined solid (3·13 g.), recyrstallised from alcohol (charcoal), yielded colourless needles, m. p. 227°, of *quinaldine hydrobromide* (Found: C, 53·4; H, 4·7; N, 6·2; Br, 35·7. $C_{10}H_{10}NBr$ requires C, 53·6; H, 4·5; N, 6·3; Br, 35·7%). The salt prepared by passing dry hydrogen bromide into an absolute alcoholic solution of the base possessed the same m. p. and mixed m. p. after recrystallisation from alcohol. Further, the picrate had m. p. 196—197°, alone or mixed with authentic quinaldine picrate (46% yield).

The final black syrup from the above preparation yielded no basic material when extracted with water.

A similar result was obtained when chloroacetone was allowed to react with quinaldine, a yield of 31% of quinaldine hydrochloride (m. p. 226°, alone and admixed) being obtained. Attempts to reduce hydrohalide formation by carrying out the reaction in solvents were equally unsuccessful.

Reaction of Iodine with α-Picoline and Acetone: Preparation of 2-Methylpyrrocoline.—To a mixture of acetone (5·8 g.) and α-picoline (30 c.c.), iodine (25·4 g.) was added portionwise. The resulting dark brown mixture, now warm, was heated on the steam-bath under reflux for 0·5 hr., and then in a vacuum to remove most of the unreacted α-picoline. Water was added to the resulting dark brown partly solid mass, followed by sodium hydrogen carbonate (*ca.* 10 g.), and the mixture slowly distilled in a current of steam. A small quantity of an oil, which was discarded, came over at first, followed by 2-methylpyrrocoline (2·5 g.; 19% yield) (confirmed by m. p. and mixed m. p.).

Reaction of Iodine with α-Picoline and Acetophenone: Preparation of 2-Phenylpyrrocoline.—To a mixture of acetophenone (8 g.) and α-picoline (12·4 g.), iodine (16·6 g.) was added portionwise. After the moderate exothermic reaction had subsided, the mixture was heated on the steam-bath for 0·75 hr. Next day the resulting thick syrup was poured into water (350 c.c.), and the heterogeneous mixture shaken with ether to remove most of the black oil. The aqueous solution was filtered through kieselguhr to remove the remainder of the oil, and then clarified with charcoal. Sodium hydrogen carbonate was added till effervescence ceased, and the liberated α-picoline extracted with ether. A portion of the final solution, after acidification, was mixed with chloroplatinic acid, to yield a buff-coloured chloroplatinate, m. p. 231° (decomp.) not depressed on admixture with an authentic specimen of phenacyl-α-picolinium chloroplatinate (m. p. 232°, decomp.). The remainder of the aqueous solution on being heated to boiling after addition of an excess of sodium hydrogen carbonate precipitated 2-phenylpyrrocoline (2·2 g.; 10% yield) (identified by m. p. and mixed m. p.).

BATTERSEA POLYTECHNIC, S.W. 11.
GLAXO LABORATORIES LTD., GREENFORD.

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237. *The Chemistry of the Pyrrocolines. Part II. Nitroso-derivatives of Some Substituted Pyrrocolines.*

By E. T. BORROWS, D. O. HOLLAND, and J. KENYON.

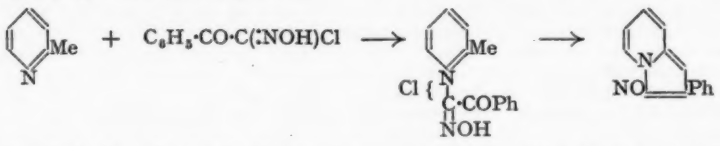
Nitrosation of several substituted pyrrocolines has been effected and the positions of the substituents established.

THERE appears to be only one recorded case of the direct introduction of a nitroso-group into the pyrrocoline nucleus: Kondo and Nischizawa (*J. Pharm. Soc. Japan*, 1936, **56**, 1; *Chem. Zentr.*, 1936, **107**, i, 4158), by the action of nitrous acid on 3-acetyl-2-methylpyrrocoline, prepared its 1-nitroso-derivative. We have applied this procedure to the preparation of the 2-phenyl analogue. Further, we have found that 1-nitroso-3-acetyl-2-methylpyrrocoline can be oxidised to α-picolinic acid *N*-oxide, thus rendering it highly probable that the nitroso-group has entered the one free position in the pyrrole ring of the pyrrocoline nucleus.

Furthermore, the method has been extended to 2-methyl- and 2-phenyl-pyrrocolines to yield two nitroso-compounds, later proved to be the 3-*nitroso*-derivatives. Oxidation showed that these also contained the nitroso-group in the pyrrole ring, for the principal product of the reaction was α-picolinic acid *N*-oxide, accompanied by benzoic acid in the case of the 2-phenylpyrrocoline derivative.

Although 3-acetyl-2-methyl- and -2-phenyl-pyrrocolines undergo deacetylation very readily (cf. Part I), the corresponding 1-nitroso-derivatives of both compounds proved more resistant to acid hydrolysis and underwent extensive decomposition as the vigour of the treatment was increased; nor was it found possible to introduce an acetyl group into 3-nitroso-derivatives of 2-methyl- and -phenyl-pyrrocoline by means of acetic anhydride or the Friedel–Crafts reaction. During the application of the latter reaction the two compounds were found to form quaternary compounds with acetyl chloride. Attention was directed therefore to the oxidation of the nitroso-derivatives of 2-methyl- and 2-phenyl-pyrrocoline with a view to orienting the groups in these compounds. The former was oxidised by hydrogen peroxide to 3-nitro-2-methylpyrrocoline (Part III). Numerous experiments were carried out before optimum conditions were established and analytically pure compounds obtained; even so, the yield was small. It was not found possible to oxidise the nitroso-derivative of the phenyl analogue to a nitro-compound, but evidence that it was the 3-nitroso-compound was furnished by the synthesis of

3-nitroso-2-phenylpyrrocoline by ring closure of ω-iso*nitrosophenacyl-α-picolinium chloride*, the preparation of which is described in the Experimental section.



Several attempts to effect ring closure in the usual manner, with cold or boiling aqueous sodium hydrogen carbonate, failed to produce more than a very small quantity of crude nitroso-compound which was accompanied by much intractable material. However, with cold aqueous 2N-sodium hydroxide ring closure occurred with surprising ease, and the overall yield of 3-nitroso-2-phenylpyrrocoline from α-picoline was 86%.

Addition of sodium hydrogen carbonate or hydroxide to an aqueous solution of ω-*iso*nitrosophenacyl-α-picolinium chloride yielded a colourless *sodio*-derivative, m. p. 86°, which contains both sodium and chloride ions. It is converted readily into ω-iso*nitrosophenacyl-α-picolinium chloroplatinate* and *picrate* by treatment of its aqueous solution with chloroplatinic and picric acid, respectively.

A feature of true unimolecular nitroso-compounds is their blue or green colour in all states of aggregation (cf. Sidgwick, " The Organic Chemistry of Nitrogen," 1942, 204) and the nitroso-compounds described herein appear to belong to this class. However, 3-nitroso-2-methylpyrrocoline and the 1-nitroso-3-acetyl derivatives of 2-methyl- and 2-phenyl-pyrrocoline produce yellow, and 3-nitroso-2-phenylpyrrocoline red solutions in dilute hydrochloric acid. Hence, as cations they do not seem to contain a true nitroso-group and resemble the *p*-nitrosoanilines (cf. Sidgwick, *op. cit.*, p. 217). Furthermore, 3-nitroso-2-methylpyrrocoline, which is very soluble in water, gave a blood-red solution, whilst the phenyl analogue, which is less soluble, is greenish-yellow. By the preparation of 1-*nitroso*-2-*methyl*-3-*ethylpyrrocoline*, which yields a red aqueous solution, it is shown that the loss of the true nitroso-structure by solution in water is not restricted to 3-nitroso-derivatives. The solubilities of these nitroso-compounds in water are not increased by the presence of alkalis.

It would seem from these results that the pyrrocoline nucleus undergoes nitrosation without difficulty by the action of sodium nitrite in acid solution, an observation in marked contrast to the rare success of such a method when applied to pyrroles and indoles.

Experimental.

(All m. p.'s are uncorrected.)

1-*Nitroso*-3-*acetyl*-2-*methylpyrrocoline*.—A solution of sodium nitrite (12 g.; 1·5 mols.) in water (50 c.c.) was slowly added to a stirred solution of 3-acetyl-2-methylpyrrocoline (20 g.) in glacial acetic acid (100 c.c.), the temperature being kept below 15°. After 15 mins. the resulting brown solution was poured into water, and the green precipitate, m. p. 138—141°, collected, washed with water until free from acetic acid, and dried in a vacuum (20 g.; 86%). 1-Nitroso-3-acetyl-2-methylpyrrocoline separates from acetone in small, dark green needles when the solution is cooled quickly, or in long, brilliant blue needles on slow cooling; both forms melt at 146—147·5° to a brown liquid [Kondo and Nischizawa, *loc. cit.*, give m. p. 146·5° (decomp.)] (Found: C, 65·4; H, 5·0; N, 14·3. Calc.: C, 65·3; H, 5·0; N, 13·9%).

The nitroso-compound (0·5 g.) was heated under reflux with acetic acid (5 c.c.) and perhydrol (5 c.c.) until the solution became almost colourless. Evaporation of the solution and extraction of the residue with methanol yielded α-picolinic acid *N*-oxide, m. p. and mixed m. p. with an authentic specimen 160° (decomp.).

1-*Nitroso*-3-*acetyl*-2-*phenylpyrrocoline*.—A solution of sodium nitrite (6 g.) in water (30 c.c.) was added dropwise to a solution of 3-acetyl-2-phenylpyrrocoline (20 g.) in glacial acetic acid (100 c.c.) the temperature of which was lowered from 20° to 10° as the reaction proceeded. The thick crystalline magma was removed by filtration and washed with water; addition of sodium hydroxide to the filtrate yielded a further crop of the same material. The *nitroso*-compound (18·7 g.; 83%) separates from aqueous alcohol in olive-green needles, m. p. 154—154·5°, which sublime at 130°/0·007 mm. (Found: C, 73·0; H, 4·8; N, 10·3. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·5; N, 10·6%). It yields a *monopicrate*, which separates from methyl cyanide in deep orange needles, m. p. 179° (decomp.) (Found: N, 14·0. $C_{22}H_{15}O_9N_5$ requires N, 14·2%).

3-*Nitroso*-2-*methylpyrrocoline*.—A solution of sodium nitrite (20 g.; 1·3 mols.) in water (100 c.c.) was added dropwise to a stirred solution of 2-methylpyrrocoline (30 g.) in hydrochloric acid (200 c.c. + 400 c.c. of water) at 0—5°. After 15 minutes the yellow solution was made alkaline by addition of sodium hydrogen carbonate, and the resulting red solution extracted three times with chloroform. Evaporation of the dried ($CaCl_2$) bright green solution in a vacuum yielded the *nitroso*-compound (30 g.; 82%), m. p. 103·5—106°; it separates from dry ethyl acetate in very dark green needles, m. p. 106—107° (Found: C, 67·3; H, 5·2; N, 17·5. $C_9H_9ON_2$ requires C, 67·5; H, 5·0; N, 17·5%). Oxidation of this compound by perhydrol in glacial acetic acid solution yielded α-picolinic acid *N*-oxide, m. p. 159—160° (decomp.) alone or mixed with an authentic specimen.

On exposure to a moist atmosphere, the nitroso-compound gradually changes into black needles possessing a blue sheen and increases in weight by 10·9%, corresponding to formation of a *monohydrate* ($C_9H_8ON_2,H_2O$ requires increase, 11·25%): it melts at 76—106°. The molecule of water is completely removed after 56 hrs. in a vacuum desiccator.

3-*Nitroso*-2-*phenylpyrrocoline*.—2-Phenylpyrrocoline (25 g.) was dissolved in concentrated hydrochloric acid (80 c.c.), and the solution diluted at 35° with water (160 c.c.). To this solution an aqueous solution of sodium nitrite (12·5 g. in 65 c.c. of water) was added dropwise with stirring; an orange-red crystalline precipitate gradually separated which became a thick magma when the mixture was cooled to room temperature. After 20 mins. the crystals were filtered off and the filtrate (I) kept for further examination. The red crystals, m. p. 200° (decomp.), separated from warm water in red needles, unchanged in m. p.; from a solution in *hot* water, however, there separated 3-*nitroso*-2-*phenylpyrrocoline semihydrochloride dihydrate*, rust-red needles, m. p. 115—116°, in poor yield. The major proportion was precipitated by the addition of 2N-sodium hydrogen carbonate (50 c.c.); the green filtrate (II) was kept. Recrystallisation of the semihydrochloride from dilute alcohol (charcoal) yielded fine needles (24·5 g.; 73%), m. p. 113—114° [Found: C, 65·2; H, 4·8; N, 10·8; Cl, 6·9. $(C_{14}H_{10}ON_2)_2,HCl,2H_2O$ requires C, 65·1; H, 4·8; N, 10·8; Cl, 6·9%). Determination of the water of crystallisation proved unsatisfactory and accordingly the active hydrogen content was determined [Found: Active H (Zerewitinoff), 0·92. Calc. for 5H: 0·97%].

Addition of an excess of sodium hydrogen carbonate to the combined filtrates I and II, followed by extraction with

ether, yielded crude **3-*nitroso*-2-*phenylpyrrocoline*** (5·6 g.; 19%), which separated from aqueous alcohol in deep green needles with a blue tint by reflected light, m. p. 97·5—98° (Found: C, 75·4; H, 4·5; N, 12·6. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5; N, 12·6%). This compound was obtained also by decomposing the above semihydrochloride with bicarbonate. The reverse of this conversion was effected by dissolving the nitroso-compound in concentrated hydrochloric acid and precipitating the semihydrochloride by addition of sodium hydrogen carbonate solution. The *picrate*, prepared in the usual way, separates from alcohol or aqueous acetone in orange-red needles, m. p. 196—197° (decomp.) (Found: C, 53·3; H, 3·5; N, 15·2. $C_{20}H_{13}O_9N_5$ requires C, 53·2; H, 2·9; N, 15·5%).

3-Nitroso-1-acetyl-2-phenylpyrrocolinium Chloride.—Acetyl chloride in excess was added to the nitroso-compound (0·25 g.) dissolved in carbon disulphide (15 c.c.), the additive *compound* separating as a red solid, m. p. 99° (decomp.) (Found: N, 9·8; Cl, 12·1. $C_{14}H_{10}ON_2,CH_3{\cdot}COCl$ requires N, 9·3; Cl, 11·8%).

Oxidation of 3-Nitroso-2-phenylpyrrocoline.—The pyrrocoline (4 g.) in glacial acetic acid (35 c.c.), oxidised with perhydrol (50 c.c.), yielded benzoic acid and α-picolinic acid *N*-oxide, m. p. 161° (decomp.) alone or mixed with an authentic specimen.

Oxidation of 3-Nitroso- to 3-Nitro-2-methylpyrrocoline.—A solution of the nitroso-compound (2 g.) in water (16 c.c.) was mixed with perhydrol (40 c.c.) and gradually heated to 65—70°; the mixture was removed from the water-bath and stirred for 10 minutes, after which the buff-coloured precipitate was removed and washed well with water and finally with a little acetone. The precipitate was discarded, and extraction of the combined filtrate and washings with chloroform yielded a green solid (0·75 g.) from which water extracted unchanged nitroso-compound (0·6 g.), leaving a dark solid (0·12 g.). The latter, in acetone solution, was passed through a small pad of alumina and there was obtained a yellow crystalline compound which separated from alcohol in yellow needles, m. p. 101—103°, alone or admixed with authentic *3-nitro-2-methylpyrrocoline* prepared by direct nitration (Found: N, 16·0. $C_6H_6O_2N_2$ requires N, 15·9%).

*ω-iso**Nitrosophenacyl-α-picolinium Chloride.***—ω-Chloro*iso*nitrosoacetophenone (10 g.) (*Org. Synth.*, 1944, **24**, 25) was gradually added to a solution of α-picoline (4·35 c.c.; 0·81 mol.) in dry benzene (150 c.c.). The resulting solution, on standing in a refrigerator, deposited the crystalline quaternary compound which, after desiccation in a vacuum over paraffin wax, weighed 13·9 g. and had m. p. 102—103° (decomp. with gas evolution). This quaternary *chloride* appeared to contain benzene of crystallisation which it readily lost on crystallisation from alcohol–ether; interlaced soft needles, m. p. 122—123° (decomp.) (Found: C, 60·6; H, 4·8; N, 10·0; Cl, 13·0. $C_{14}H_{13}O_2N_2Cl$ requires C, 60·7; H, 4·7; N, 10·1; Cl, 12·8%).

Addition of chloroplatinic acid to an aqueous solution of the quaternary chloride precipitated the *chloroplatinate* as a buff-coloured powder, m. p. 199° (decomp.) [Found: N, 6·2; Pt, 21·9. $(C_{14}H_{13}O_2N_2)_2PtCl_6$ requires N, 6·3; Pt, 21·9%]. The *picrate* was precipitated from an alcoholic solution of the quaternary chloride, on addition of picric acid in the same solvent, as yellow crystalline leaflets, m. p. 176° (decomp.) (Found: Cl, 51·3; H, 3·5; N, 14·8. $C_{20}H_{15}O_9N_5$ requires C, 51·2; H, 3·2; N, 14·9%).

*Formation of 3-Nitroso-2-phenylpyrrocoline from ω-iso**Nitrosophenacyl-α-picolinium Chloride.***—A solution of the quaternary chloride (8 g.) in water (60 c.c.) was covered with ether (30 c.c.) and then mixed with sodium hydroxide (40 c.c., 2N), and the whole well shaken at intervals during 30 mins. Filtration removed the crystalline precipitate of 3-nitroso-2-phenylpyrrocoline (4·2 g., 71%), m. p. 97—98°, which had been rapidly formed. The ethereal layer yielded a further 0·88 g. of the same product contaminated with α-picoline. The 3-nitroso-2-phenylpyrrocoline separated from aqueous alcohol in dark green needles, m. p. 97·5—98° alone, or when mixed with the compound produced by nitrosation of 2-phenylpyrrocoline (Found: C, 75·4; H, 4·9; N, 12·6%). Further confirmation was afforded by the conversion of this 3-nitroso-2-phenylpyrrocoline into its picrate (Found: N, 15·3%), and its semihydrochloride, the properties of which were identical with those of the compounds prepared as described above.

1-Nitroso-2-methyl-3-ethylpyrrocoline.—A solution of sodium nitrite (2·4 g.) in water (20 c.c.) was slowly added to a stirred solution, at 0°, of 2-methyl-3-ethylpyrrocoline (5 g.) in hydrochloric acid (15 c.c. + water 30 c.c.). After 30 minutes the solution was made alkaline with sodium hydroxide and the red solution, entraining an oil having the odour of unchanged pyrrocoline, extracted with chloroform. A green oily solid (5·6 g.) was thus obtained, which after being washed with ligroin and crystallised from benzene, yielded *1-nitroso-2-methyl-3-ethylpyrrocoline* (2·6 g.), very dark green microscopic irregular crystals, m. p. 110—111° (Found: C, 70·3; H, 6·3; N, 15·4. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%). Exposure to a moist atmosphere converts this nitroso-derivative into a red-brown *trihydrate* which melts indefinitely at 52—86°, the gain in weight being 28·6% ($C_{11}H_{12}ON_2,3H_2O$ requires gain, 28·7%). Exposure of this to a dry atmosphere for about 48 hours regenerated the anhydrous nitroso-compound.

BATTERSEA POLYTECHNIC, S.W. 11.
GLAXO LABORATORIES LTD., GREENFORD.

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238. *The Chemistry of the Pyrrocolines. Part III. Nitration.*

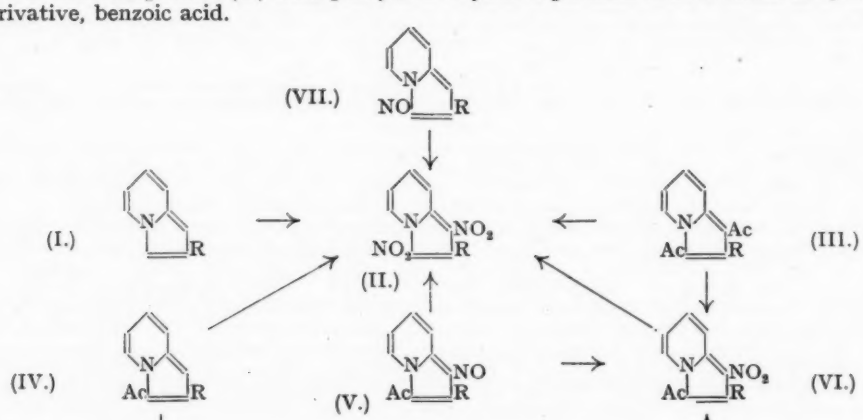
By E. T. BORROWS, D. O. HOLLAND, and J. KENYON.

2-Methyl- and 2-phenyl-pyrrocolines and their 3-acetyl and 1:3-diacetyl derivatives have been nitrated to yield a variety of nitro-compounds in which the positions of the substituents have been determined.

ACCORDING to Scholtz (*Ber.*, 1912, **45**, 1718) pyrrocoline cannot be nitrated directly because of its sensitivity to oxidising agents, but the 1 : 3-diacetyl derivative (cf. Part I) can be nitrated progressively in acetic acid with 25% and with concentrated nitric acid to yield respectively a nitro-acetyl- and a dinitro-pyrrocoline. In a similar manner Diels and Meyer (*Annalen*, 1934, **513**, 129) prepared methyl 1-nitropyrrocoline-2 : 3-dicarboxylate from methyl 1-methoxycarbomethoxymethylpyrrocoline-2 : 3-dicarboxylate. Pyrrocoline would appear to behave in this respect similarly to pyrrole.

When 2-methyl- and 2-phenyl-pyrrocoline were allowed to react with nitric acid under a variety of conditions considerable oxidation took place with the formation, in the main, of water-soluble products. This appeared to be particularly the case when the reaction was carried out at moderate temperatures, oxidation proceeding slowly with little evidence of nitration. Nevertheless, it has proved possible to convert these pyrrocolines (I) by the action of hot nitric acid into 1 : 3-*dinitro*-derivatives (II) : in the case of the 2-methyl compound nitration resulted even with hot dilute nitric acid, but it was effected best by concentrated nitric acid in acetic acid containing a few drops of concentrated sulphuric acid. These dinitro-compounds were better

prepared from the respective 3-acetyl and 1 : 3-diacetyl derivatives (IV and III) by essentially the same method of dinitration as that described by Scholtz (*loc. cit.*) or, in the case of the monoacetyl compounds, by direct action of cold nitric acid; the 3-nitroso-derivatives of 2-methyl- and 2-phenyl-pyrrocoline (VII) were converted also by the former method into the dinitro-compounds (II). The structures were assigned on evidence afforded by oxidation of both compounds (II) with perhydrol to yield α-picolinic acid *N*-oxide and, in the case of the 2-phenyl derivative, benzoic acid.



The conditions described by Scholtz (*loc. cit.*) for the mononitration of 1 : 3-diacetylpyrrocoline were applied to the 2-methyl and the 2-phenyl compound (IV), 1-*nitro*-3-*acetyl* derivatives (VI) being obtained. The reaction proceeded readily in the case of (IV, R = Ph), but with (IV, R = Me) considerable decomposition took place and only a very poor yield of the desired product was obtained accompanied by a little 1 : 3-dinitro-2-methylpyrrocoline (II, R = Me). On attempting the reaction under a variety of conditions on 3-acetyl-2-phenylpyrrocoline no tractable product other than 2-phenylpyrrocoline or its 1 : 3-dinitro-derivative could be isolated; this was probably due to the extreme mobility of the acetyl group in this compound. The 2-methyl analogue (IV, R = Me) likewise failed to yield the 1-nitro-compound on application of this method, but treatment under carefully regulated conditions in hot acetic acid with concentrated nitric acid gave rise to (VI, R = Me) in 36% yield and some dinitro-compound. It seems likely from this experiment that in the reaction of nitric acid in acetic acid on the monoacetyl compounds (IV) to form (II) the nitro-acetyl compounds (VI) are intermediates; indeed, it was shown that the latter could be converted into (II) by further treatment with this reagent. This conversion established that the nitro-group in (VI) is attached to the pyrrole ring, and its position was determined finally by the preparation of (VI) from the 1-nitroso-3-acetyl derivatives (V) of 2-methyl- and 2-phenyl-pyrrocoline (Part II) by oxidation with perhydrol. By analogy, the nitroacetylpyrrocoline prepared by Scholtz (*loc. cit.*) would seem to be the 1-nitro-3-acetyl derivative. The nitroacetyl pyrrocolines (VI), like the nitroso-derivatives (V) (Part II), are resistant to acid hydrolysis, and no satisfactory method for their deacetylation has been devised.

1-Nitroso-3-acetyl-2-phenylpyrrocoline (V, R = Ph) was also converted into (II, R = Ph) as independent evidence that the nitroso-group is attached to the pyrrole ring.

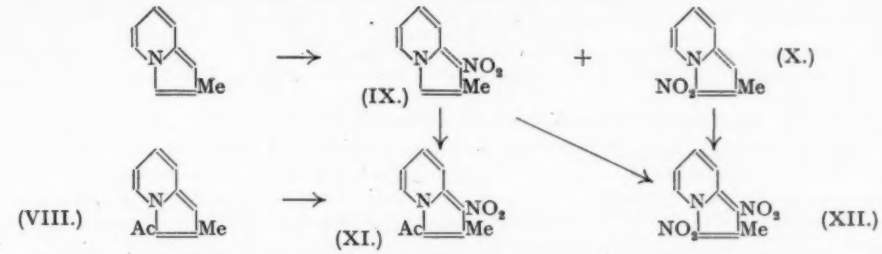
The study on nitration was continued by attempting the reaction in concentrated sulphuric acid. In this way 2-methylpyrrocoline gives two mononitro-compounds and a little dinitro-compound (XII). Of the former, only that produced in major proportion (m. p. 154·5—155·5°; 82% yield) could be acetylated by acetic anhydride, and then with some difficulty (5 days' refluxing), to yield 1-nitro-3-acetyl-2-methylpyrrocoline (XI). The other mono-nitro-compound, m. p. 103—104° (1·5% yield), could not be acetylated and was recovered unchanged even after treatment at 200° with acetic anhydride, to which it showed a marked stability. The acetylation of the nitro-compound, m. p. 154·5—155·5°, and its oxidation to α-picolinic acid *N*-oxide afford unequivocal proof that it is 1-*nitro*-2-*methylpyrrocoline* (IX), and the isomeric product, m. p. 103—104°, is therefore the 3-*nitro*-derivative (X). These compounds behaved quite differently on attempted further nitration. The 3-nitro-compound (X), similarly to 3-nitroso-2-methylpyrrocoline (VII, R = Me), is readily converted by the action of a hot mixture of concentrated nitric acid and acetic acid into (XII), which confirms the suggested structure. On the other hand, the 1-nitro-isomer (IX) could not be nitrated by this procedure or by a mixture of nitric and sulphuric acids, and the reaction was eventually effected by the method employed for the dinitration of 2-methylpyrrocoline.

This preferential nitration of the pyrrocoline structure in position 1 is in marked contrast to the facile 3-nitrosation reported previously (Part II).

Dhont and Wibaut (*Rec. Trav. chim.*, 1943, **62**, 177) record that nitration of *N*-phenylpyrrole by nitric acid and acetic anhydride yields the 2- and the 3-nitro-derivative, but application of this procedure to 2-methyl-pyrrocoline has yielded an intractable tar as the main product.

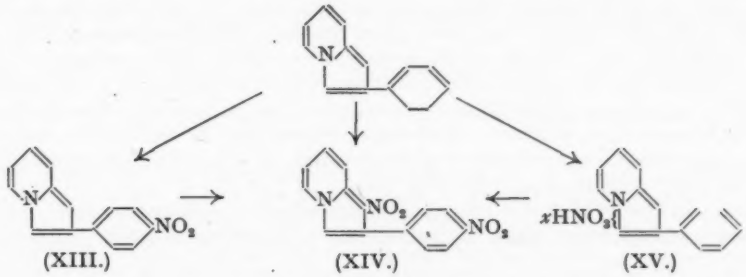
On addition of an ethereal solution of nitric acid to 3-acetyl-2-methylpyrrocoline in the same solvent a

dinitrate separated which could be dehydrated by boiling acetic acid to give 1-nitro-3-acetyl-2-methylpyrrocoline (XI) in poor yield. The latter compound was formed in good yield (59%) along with some (XII) when the acetyl derivative in cold sulphuric acid solution was treated with nitric acid.



In several experiments the accompanying 1 : 3-dinitro-2-methylpyrrocoline (XII) could only be separated from the principal nitro-products by chromatography of the yellow solution of the mixture in dry benzene on a column of alumina. Under such conditions (XII) exhibited a very striking phenomenon, for it produced a red chromatogram, quite distinct from the yellow ones produced by the other nitro-compounds. The depth of the red colour appeared to be dependent on the character of the particular batch of alumina, and indeed one batch produced a yellow chromatogram in place of the usual red one.

Addition of 1 mol. of nitric acid to 2-phenylpyrrocoline in concentrated sulphuric acid solution at 0° yielded a product from which a mononitro-compound was isolated in 41% yield, accompanied by a much smaller quantity of a dinitro-compound (m. p. 235·5—236°). The former was shown by oxidation to be 2-p-*nitrophenylpyrrocoline* (XIII), for it yielded as major products α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid. An identical mononitro-compound (XIII) was also prepared by nitration in phosphoric acid solution or by the action of sodium nitrate and sulphuric acid; these methods did not appear to offer any advantage over that just described. The dinitro-compound, m. p. 235·5—236°, was identified later by comparison with a specimen of 1-*nitro*-2-p-*nitrophenylpyrrocoline* (XIV) and it is prepared more conveniently by the further nitration of 2-*p*-nitrophenylpyrrocoline or by the dinitration of 2-phenylpyrrocoline with nitric acid.

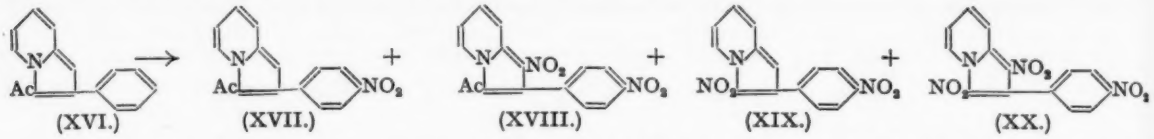


Little tractable material resulted from any of the numerous experiments essayed to nitrate 2-phenylpyrrocoline in acetic acid solution by addition of nitric acid of various concentrations : owing to the low solubility of the pyrrocoline most of these experiments were carried out on the steam-bath. Subsequently it was discovered that the pyrrocoline would slowly dissolve in acetic acid at room temperature in the presence of 1 mol. of concentrated nitric acid to give a yellow solution from which it separated unchanged on dilution with water : considerable oxidation of the pyrrocoline appears to take place on keeping the solution for 24 hrs. at room temperature. Addition of a second mol. of concentrated nitric acid, however, to the original yellow solution immediately precipitated a *nitrate* of 2-phenylpyrrocoline in monoclinic needles which appear to contain *ca.* 1·8 mols. of nitric acid. Dehydration of the nitrate was effected satisfactorily only by sulphuric acid, 1-nitro-2-*p*-nitrophenylpyrrocoline (XIV) being obtained in 40% yield. The latter compound yielded on oxidation α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid; but numerous attempts, described later, failed to determine unambiguously the position of the second nitro-group. However, it has been shown already that nitration of 2-methylpyrrocoline under conditions identical with those used for the preparation of (XIV) yielded 1-nitro-2-methylpyrrocoline and hence it is highly probable that the structure assigned to (XIV) is correct.

Although nitration of 2-phenylpyrrocoline in sulphuric acid preferentially occurred at the para-position in the benzene ring in contrast to the facile nitration at position 3 (Part II), it is not entirely unexpected, for similar treatment of *N*-phenylpyrrole yields *N*-*p*-nitrophenylpyrrole (Dhont and Wibaut, *loc. cit.*).

Results of the nitration of 2-phenylpyrrocoline in sulphuric acid solution suggested a method of preparing, from (XVI), 1-nitro-3-acetyl-2-*p*-nitrophenylpyrrocoline (XVIII), of possible value in the orientation of (XIV), assuming that the labile acetyl group in (XVI) would not be removed too readily under the experimental conditions. For this investigation 1 or 2 mols. of nitric acid were employed and in both cases a mixture of at least four nitro-compounds was obtained, the separation of which proved laborious; a difficulty enhanced by

the inherent light-sensitivity of three of the compounds (XVII, XIX, and XX). All three are yellow crystalline solids which rapidly turn green when exposed to air and sunlight.



(XVI.) (XVII.) (XVIII.) (XIX.) (XX.)

The respective yields of the nitro-compounds are dependent on the amount of nitric acid employed, but with 2 mols. a larger total quantity of crude products resulted in addition to the anticipated increase in polynitration. Three of the products, 1-*nitro*-3-*acetyl*- (XVIII), 3-*nitro*- (XIX), and 1 : 3-*dinitro*-2-p-*nitrophenylpyrrocoline* (XX), on oxidation gave rise with varying ease to α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid. The fourth, 3-*acetyl*-2-p-*nitrophenylpyrrocoline* (XVII), proved to be identical with the product of the acetylation of 2-*p*-nitrophenylpyrrocoline (XIII), whence its formulation follows; the acetyl group in (XVII) appears to be slightly less labile to hydrolysis than that in (XVI). The preparation of (XVII) from (XIII) by a short period of refluxing with sodium acetate–acetic anhydride indicates that the difficult acetylation of nitro-pyrrocolines is restricted to those with the nitro-group attached to the pyrrole ring.

Attention was directed to the acetylation of the 1-nitro- (XIV) and the 3-nitro-derivative (XIX) of 2-*p*-nitrophenylpyrrocoline, following the failure to effect deacetylation of (XVIII) under a variety of conditions. Whereas the 1-nitro-compound (XIV) can be recovered, accompanied by charred material, after 48 hrs.' heating at 200° with acetic anhydride or after being heated under reflux with acetic anhydride and sodium acetate for 2—6 days, the 3-nitro-isomeride (XIX) under similar conditions yields a yellow intractable oil along with unchanged material. However, on one occasion a small quantity (*ca.* 10 mg. from 0·5 g.) of crystalline yellow powder, m. p. 234—235°, was separated from (XIX) after 5 days' refluxing. This product could not be purified in sufficient quantity for analysis and several attempts to prepare more were unsuccessful, but it depressed the m. p. on admixture with (XIV), m. p. 235·5—236°, and (XX), m. p. 234—235° (decomp.).

In view of this inconclusive result an attempt was made to synthesise 3-nitro-2-phenylpyrrocoline from ω-nitrobromoacetophenone and α-picoline, by a method similar to that employed successfully for the 3-nitroso-derivative (Part II). ω-Nitrobromoacetophenone was prepared by the bromination (Thiele, *Annalen*, 1902, **325**, 13) of ω-nitroacetophenone which was prepared by the method of Jaberkowitsch (*J. pr. Chem.*, 1935, **142**, 37; cf. Fujise *et al.*, *Ber.*, 1935, **68**, 1272). The latter method for nitroacetophenone proved more expeditious than that described by Thiele (*loc. cit.*) and gave good yields. The bromo-ketone reacted slowly at room temperature with α-picoline to form a syrup which appeared to contain little quaternary compound but a large portion of a salt of α-picoline (probably hydrobromide) and a little benzoic acid; attempted ring closure under a variety of conditions on the aqueous extract of the syrup, after removal of α-picoline and benzoic acid, yielded a negligible quantity of red product. The formation of benzoic acid recalls the recorded loss of acyl groups from quaternary compounds prepared from pyridine or α-picoline and α-halogeno-β-diketones (cf. Part I; also Krohnke and Timmler, *Ber.*, 1936, **69**, 614).

The direct nitration of the pyrrocoline ring, herein described, would appear to show once more that this interesting ring system is not so closely allied in its properties to pyrrole and indole as might be anticipated from its structure.

Experimental.

All m. p.'s are uncorrected. Savory and Moore standardised Brockmann alumina was employed for all chromatographic purifications. The ligroin used had b. p. 60—80°, and the nitric acid *d* 1·4 unless otherwise stated.

1 : 3-*Dinitro*-2-*methylpyrrocoline*.—(a) *From* 2-*methylpyrrocoline*. To a solution of the latter (0·5 g.) in acetic acid (5 c.c.) was added concentrated sulphuric acid (0·25 c.c.) followed by nitric acid (1 c.c.). The mixture was heated carefully over a flame until a vigorous reaction set in which was allowed to continue for *ca.* 2 mins.; the mixture was then poured into water, and the yellow precipitate (0·19 g.; 22%), m. p. 214—215° (decomp.), filtered off, washed, dried, and recrystallised from acetone to yield 1 : 3-*dinitro*-2-*methylpyrrocoline* as a yellow microcrystalline powder, m. p. 218—219° (decomp.) (Found: N, 19·0. $C_9H_7O_4N_3$ requires N, 18·8%). The omission of sulphuric acid in this preparation gave a much cruder product and a low yield of the dinitro-compound.

(b) *From* 3-*acetyl*-2-*methylpyrrolocine*. When the acetyl compound (5 g.) in acetic acid (50 c.c.) was mixed with nitric acid (38 c.c.) a spontaneous reaction set in with evolution of nitrous fumes and deposition of a bright yellow solid. The reaction mixture was heated for 5 mins. on the steam-bath, diluted with water, filtered, and the solid product washed and dried (3·65 g.; 58%), m. p. 218—219° (decomp.); it separated from acetone as a yellow microcrystalline powder with unaltered m. p. (Found: C, 48·9; H, 3·3; N, 19·2. $C_9H_7O_4N_3$ requires C, 48·9; H, 3·2; N, 18·8%). An identical product was obtained when the acetyl compound was dissolved in nitric acid; it separated from the solution after 1 min.

(c) *From* 1 : 3-*diacetyl*-2-*methylpyrrocoline*. A solution of the latter (0·2 g.) in acetic acid (2 c.c.) and nitric acid (1·5 c.c.) was heated for 10 mins. on the steam-bath. The dinitro-compound separated almost immediately and was filtered off after dilution of the reaction mixture with water and crystallised from acetone, m. p. 218—219° (decomp.) alone and admixed with the compound prepared by procedure (*a*); yield 0·[illegible] g.; 59%.

(d) *From* 1-*nitro*-3-*acetyl*-2-*methylpyrrocoline*. This compound (0·5 g.) yielded the dinitro-compound (0·5 g.), m. p. 218—219° (decomp.), almost quantitatively when treated as in (c).

(e) *From* 3-*nitroso*-2-*methylpyrrocoline*. This compound (0·25 g.), on treatment as in (c), also yielded the dinitro-compound (0·12 g.), m. p. 218—219° (decomp.) (Found: N, 18·4%).

A solution of 1 : 3-dinitro-2-methylpyrrocoline (0·3 g.) in acetic acid (5 c.c.) and perhydrol (5 c.c.), heated for 2 hrs., gave α-picolinic acid *N*-oxide, m. p. and mixed m. p. 162° (decomp.).

1 : 3-*Dinitro*-2-*phenylpyrrocoline*.—(a) *From* 2-*phenylpyrrocoline*. A solution of the pyrrocoline (2 g.) in nitric acid (10 c.c.) was warmed cautiously over a free flame until a vigorous reaction set in which was controlled by immediate

cooling. Heating was then resumed until the active evolution of nitrous fumes recommenced, and the mixture was then cooled and poured on ice. The washed and dried reddish-orange precipitate (0·8 g.) was extracted with hot ethyl acetate (100 c.c.) to remove insoluble material, which was neglected. The ethyl acetate solution was heated with charcoal and cooled, greenish-orange crystals (0·38 g.; m. p. 233—238°) separating; concentration of the filtrate yielded a second crop (0·2 g.). The combined crops were recrystallised from acetic acid to give 1 : 3-*dinitro*-2-*phenylpyrrocoline* (0·4 g.; 14%) as fine yellow needles, m. p. 246—247°, having a green tint. The green colour was removed by sublimation at 180—190°/0·02 mm. (Found : N, 14·9. $C_{14}H_9O_4N_3$ requires N, 14·8%).

(b) *From* 3-*acetyl*-2-*phenylpyrrocoline*. This reaction was effected essentially as described above for the 2-methyl analogue, the acetyl compound (0·2 g.) giving the dinitro-compound (0·15 g.; 51%) as yellow needles, m. p. 246—247° alone and admixed with the compound obtained in (a) (Found : C, 59·5; H, 3·4; N, 14·5. $C_{14}H_9O_4N_3$ requires C, 59·4; H, 3·2; N, 14·8%). It can also be prepared in 48% yield by solution of the acetyl compound in nitric acid at room temperature.

From (c) 1 : 3-*diacetyl*-, (d) 1-*nitro*-3-*acetyl*-, *and* (e) 1-*nitroso*-3-*acetyl*-2-*phenylpyrrocoline*. These reactions were carried out essentially by the procedures already described. The dinitro-compound was obtained in yields of 78%, 66%, and 67%, respectively, from these compounds.

(f) *From* 3-*nitroso*-2-*phenylpyrrocoline*. A solution of this compound (0·2 g.) in acetic acid (2 c.c.) with nitric acid (1 c.c.) was heated for 10 mins. on the steam-bath, cooled, and diluted with water. The small amount (0·1 g.) of precipitated material was collected, purified, and characterised in the usual manner.

Oxidation of 1 : 3-dinitro-2-phenylpyrrocoline (1 g.) in acetic acid (20 c.c.) with perhydrol (15 c.c.) for 2 hrs. on the steam-bath yielded α-picolinic acid *N*-oxide (0·2 g.), m. p. 162° (decomp.), and benzoic acid (0·25 g.).

Preparation of 1-*Nitro*-3-*acetyl*-2-*methylpyrrocoline*.—To a solution of 3-acetyl-2-methylpyrrocoline (3 g.) in acetic acid (30 c.c.) at 90° nitric acid (2·25 c.c.) was added dropwise at a rapid rate; a vigorous reaction set in with evolution of nitrous fumes. After the reaction had proceeded for 30 seconds the mixture was poured into water. The orange-yellow precipitate (2·3 g.) was washed, dried, and dissolved in boiling ethyl acetate (50 c.c.), leaving a little black insoluble material. The deeply coloured solution was heated with charcoal, filtered, and concentrated; the residue, dissolved in acetone (50 c.c.), was passed through a column of alumina to yield a narrow brown, a deep red, and a wide bright yellow chromatogram. The last was eluted with acetone to yield a yellow solid (1·75 g.), m. p. 134—136°, which was a mixture of 1-nitro-3-acetyl- and 1 : 3-dinitro-2-methylpyrrocoline inseparable by fractional crystallisation.

The mixture was dissolved in dry benzene and passed through a column of alumina, an orange-red chromatogram being formed at the lower end of a yellow band; these were separated by extrusion of the column and cutting at the appropriate point. The orange-red portion was eluted with acetone–alcohol, and the extracted material crystallised from acetone, 1 : 3-dinitro-2-methylpyrrocoline being obtained as yellow needles (4% yield), m. p. 218—219° (decomp.). From the eluate of the yellow chromatogram 1-*nitro*-3-*acetyl*-2-*methylpyrrocoline* (1·6 g.; 36%) was isolated; it crystallised from alcohol in yellow needles, m. p. 140·5—141° (Found : C, 60·1; H, 4·5; N, 12·8. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%).

When the reaction of 1 : 3-diacetyl-2-methylpyrrocoline (0·5 g.) in acetic acid (5 c.c.) with 25% nitric acid (2·5 c.c.) was allowed to proceed for 24 hrs. at room temperature both nitro-compounds were produced but in very low yields.

The 2 : 4-*dinitrophenylhydrazone* of 1-nitro-3-acetyl-2-methylpyrrocoline, prepared by mixing alcoholic solutions of the reagents, separated as a scarlet, crystalline powder, m. p. 276—277° (decomp.) (Found : N, 20·8. $C_{17}H_{14}O_6N_6$ requires N, 21·1%).

Oxidation of the nitroacetyl compound (0·4 g.) in refluxing acetic acid (5 c.c.) with perhydrol (5 c.c.) for 1 hr. yielded α-picolinic acid *N*-oxide, m. p. 162° (decomp.).

Oxidation of 1-*Nitroso*-3-*acetyl*-2-*methylpyrrocoline*.—When a solution of the pyrrocoline (1 g.) in acetic acid (20 c.c.) and perhydrol (5 c.c.) was heated to boiling, a reaction set in which was allowed to proceed unaided for 20 seconds. The mixture was then cooled, poured into water, and the yellow precipitate collected, washed and dried. Crystallisation from ethyl acetate (charcoal) yielded the nitro-compound, yellow needles, m. p. 140·5—141° alone and admixed with that prepared as above (Found : C, 60·35; H, 4·5; N, 13·1%). The 2 : 4-dinitrophenylhydrazone also was identical with that described above, m. p. 276—277° (decomp.) alone and admixed.

Preparation of 1-*Nitro*-3-*acetyl*-2-*phenylpyrrocoline*.—A solution of 1 : 3-diacetyl-2-phenylpyrrocoline (4·5 g.) in a mixture of 25% nitric acid (22·5 c.c.) and acetic acid (45 c.c.) during 2 days at room temperature deposited 1-*nitro*-3-*acetyl*-2-*phenylpyrrocoline* as yellow needles. The reaction mixture was diluted with water, and the solid product crystallised from alcohol; bright yellow needles (2·3 g.; 50%), m. p. 169° (Found : C, 68·6; H, 4·3; N, 10·3. $C_{16}H_{13}O_3N_2$ requires C, 68·5; H, 4·3; N, 10·0%). The 2 : 4-*dinitrophenylhydrazone* slowly separated as red crystalline platelets when an alcoholic solution of the nitroacetyl compound and Brady's reagent was heated; it recrystallised from methyl cyanide as red needles, m. p. 253° (decomp.) (Found : N, 18·05. $C_{22}H_{16}O_6N_6$ requires N, 18·25%).

Oxidation of 1-*Nitroso*-3-*acetyl*-2-*phenylpyrrocoline*.—When a solution of the nitroso-derivative (0·5 g.) in a mixture of acetic acid (7 c.c.) and perhydrol (8 c.c.) was brought to the boil it continued boiling of its own accord for 4 mins.; the solution was then cooled and the nitro-compound (0·25 g.; 47%), m. p. 168—169°, separated; it recrystallised from acetic acid as yellow needles, m. p. 169° alone and admixed with the specimen prepared as described above (Found : C, 68·2; H, 4·0; N, 10·5%). Its identity was confirmed by the preparation of the 2 : 4-dinitrophenylhydrazone, m. p. 253° (decomp.) alone and admixed (Found : N, 18·0%).

Nitration of 2-*Methylpyrrocoline in Sulphuric Acid*.—Nitric acid (12 c.c.) was added slowly to a stirred solution of 2-methylpyrrocoline (12 g.) in concentrated sulphuric acid (35 c.c.) at 0°. After 5 mins. the resultant dark red solution was poured on crushed ice, and the orange-red precipitate immediately filtered off, washed thoroughly, and dried in a vacuum; yield 11·3 g., m. p. 149—153°. The product deteriorated rapidly when it was not thoroughly washed with water before drying.

The solid was dissolved in acetone (400 c.c.) and the filtered brown solution passed through a column of alumina. A wide yellow chromatogram rapidly developed and spread down the column, leaving a dark brown zone at the top. The former was eluted with acetone, and the eluate concentrated to yield a bright yellow solid, m. p. 154—155° (10·0 g.; 62%). Recrystallisation of this from acetic acid gave 1-*nitro*-2-*methylpyrrocoline*, yellow needles, m. p. 154·5—155·5° (Found : C, 61·6; H, 4·5, N, 16·2. $C_6H_6O_2N_2$ requires C, 61·3; H, 4·6; N, 15·9%).

The original acid filtrate was made alkaline by careful addition of 40% sodium hydroxide, and the resulting dark precipitate was filtered off, washed with water, and dried in a vacuum (3·0 g.). This was subjected to steam-distillation to remove 2-methylpyrrocoline (1·6 g.) and the distillation was discontinued when a yellow solid commenced to distil. The residual bright yellow aqueous solution was decanted from a considerable quantity of black tar which was extracted with several portions of boiling water until the aqueous extracts were colourless. The combined aqueous solutions were extracted with ether to yield a yellow solid (0·25 g.; 1·5%) which, after recrystallisation from aqueous alcohol gave 3-*nitro*-2-*methylpyrrocoline* as yellow needles, m. p. 103—104° (Found : C, 61·0; H, 4·5; N, 16·5%).

Oxidation of 1-nitro-2-methylpyrrocoline (0·5 g.) with a mixture of perhydrol (5 c.c.) and acetic acid (10 c.c.) for 45

mins. under reflux yielded α-picolinic acid *N*-oxide (0·15 g.), m. p. 159·5° (decomp.) alone and on admixture with an authentic specimen.

On one occasion a small quantity of 1 : 3-dinitro-2-methylpyrrocoline was isolated. This was effected by chromatography of a portion of the crude product dissolved in dry benzene on a column of alumina; a distinct red chromatogram was obtained quite separate from the larger yellow one containing the above two mononitro-compounds. The dinitropyrrocoline was removed and identified in the usual manner.

Preparation of 1 : 3-*Dinitro-2-methylpyrrocoline.*—(a) *From* 1-*nitro-2-methylpyrrocoline.* A solution of the 1-nitro-compound (0·5 g.) in acetic acid (10 c.c.) was mixed with concentrated sulphuric acid (0·5 c.c.) and nitric acid (0·8 c.c.), and heated carefully over a small flame until a reaction set in which was allowed to continue for 1 min. away from the heat source; the mixture was then poured into water. The precipitated brown solid (0·15 g.), after recrystallising from acetone (charcoal), yielded 1 : 3-dinitro-2-methylpyrrocoline, m. p. 218—219° (decomp.) alone and on admixture with an authentic specimen.

(b) *From* 3-*nitro-2-methylpyrrocoline.* A solution of the 3-nitro-compound (0·05 g.) in nitric acid (0·5 c.c.) and acetic acid (1 c.c.) was warmed on the steam-bath for 1 min., diluted with water, and the precipitate, m. p. 217—218°, (decomp.), recrystallised from acetone, a yellow microcrystalline powder, m. p. 218—219° (decomp.) alone and when mixed with an authentic specimen of 1 : 3-dinitro-2-methylpyrrocoline, being obtained.

Acetylation of 1-*Nitro-2-methylpyrrocoline.*—A solution of the nitro-compound (1 g.) and fused sodium acetate (2 g.) in acetic anhydride (25 c.c.) was refluxed for 5 days, mixed with alcohol, and evaporated to dryness on a steam-bath. Trituration of the dark residue with water yielded an oil which solidified; this was washed with water, dried, and dissolved in benzene. The benzene solution, filtered from black insoluble material (0·4 g.), was poured down a column of alumina, and a bright yellow chromatogram that spread rapidly down the column was obtained. The extruded column of alumina was cut to remove two narrow brown chromatograms at the top, and the remaining yellow one was eluted with alcohol. The alcoholic eluate was concentrated to leave a sticky yellow solid (0·8 g.), m. p. 85—115°, which by fractional crystallisation from alcohol was separated into more soluble unchanged 1-nitro-2-methylpyrrocoline (0·4 g.) and 1-nitro-3-acetyl-2-methylpyrrocoline (0·2 g.), m. p. 140·5—141° alone and on admixture with the product prepared by direct nitration (Found : N, 12·3%). The 2 : 4-dinitrophenylhydrazone, prepared in the usual manner, had m. p. 276—277° (decomp.) alone and on admixture with specimens prepared by other routes.

3-*Acetyl-2-methylpyrrocoline Nitrate.*—On addition of a solution of fuming nitric acid (0·3 c.c.) in ether (10 c.c.) to 3-acetyl-2-methylpyrrocoline (0·5 g.) in ether (10 c.c.), a purple colour developed and a pale green solid (0·18 g.) separated. The solid, which was washed with ether, decomposed at 115—116° with explosive violence but was quite stable at 100° (30 mins.) (Found : N, 14·2. $C_{11}H_{11}ON,2HNO_3$ requires N, 14·1%). Dehydration of this *salt* in boiling toluene was unsatisfactory, but in acetic acid it yielded, after 1 min.'s boiling, a dark brown solid, from which a small quantity of 1-nitro-3-acetyl-2-methylpyrrocoline was isolated, m. p. 140·5—141° alone and on admixture with an authentic specimen.

Nitration of 3-*Acetyl-2-methylpyrrocoline in Sulphuric Acid.*—A solution of the acetyl compound (10 g.) in concentrated sulphuric acid (100 c.c.) was stirred and kept at 0° during the dropwise addition of a mixture of nitric acid (4·5 c.c.) and sulphuric acid (20 c.c.). After 15 mins. the mixture was poured on crushed ice, and the precipitated yellow solid filtered off, washed, and dried in a vacuum; yield 9·6 g., m. p. 132—136°. The yellow solid was dissolved in cold acetone (350 c.c.), and the red brown solution filtered down a column of alumina (27 × 3 cm.). The bright yellow chromatogram that rapidly swept down the column was completely eluted, and the dark brown band remaining at the top of the column was discarded. The acetone eluate on concentration yielded an orange-yellow solid (9·0 g.), m. p. 135—136°, which was dissolved in dry benzene and chromatographed on a column of alumina in a similar manner to that employed in the preparation of 1-nitro-3-acetyl-2-methylpyrrocoline by the action of nitric acid in acetic acid. By this procedure 1-nitro-3-acetyl- (7·5 g.; 59%) and 1 : 3-dinitro-2-methylpyrrocoline (0·79 g.; 6%) were isolated and identified in the usual manner.

Nitration of 2-*Phenylpyrrocoline in Concentrated Sulphuric Acid.*—2-Phenylpyrrocoline (10 g.) was added with stirring to concentrated sulphuric acid (60 c.c.) cooled in ice-salt, and the temperature was kept at 0° during the dropwise addition (30 mins.) of nitric acid (3·5 c.c.). The orange-yellow product [8·7 g.; m. p. 218—230° (decomp.)] precipitated by pouring the thick reaction mixture on crushed ice was filtered off immediately and washed repeatedly before being dried in a vacuum. The dried material, crystallised from ethyl acetate (charcoal), yielded 2-p-*nitrophenylpyrrocoline* (5·8 g.), m. p. 245·5—246° (decomp.), which separated from methyl cyanide in yellow platelets (5 g.; 41%), m. p. 250—251° (decomp.) (Found: C, 70·8; H, 4·35; N, 12·2. $C_{14}H_{10}O_2N_2$ requires C, 70·6; H, 4·2; N, 11·8%). The original ethyl acetate mother-liquor was concentrated to a small volume, filtered through a column of alumina, and the eluate and washings were concentrated. The residue yielded, by fractional crystallisation from acetone, 30 mg. of 1-nitro-2-*p*-nitrophenylpyrrocoline as yellow needles, m. p. 235·5—236° alone and on admixture with an authentic specimen.

2-*p*-Nitrophenylpyrrocoline, refluxed for 3 hrs. in glacial acetic acid (20 c.c.) with perhydrol, yielded α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid.

2-*p*-Nitrophenylpyrrocoline was obtained in 37% yield when a mixture of 2-phenylpyrrocoline (1·2 g.) in phosphoric acid (25 c.c.) and nitric acid (0·41 c.c.) was left for 16 hrs. at room temperature. Trituration of 2-phenylpyrrocoline (0·5 g.) in concentrated sulphuric acid (2 c.c.) with sodium nitrate (0·24 g.) in the cold and finally on the steam-bath gave rise to 2-*p*-nitrophenylpyrrocoline (0·2 g.; 31%), m. p. 250—251° (decomp.) alone and admixed with an authentic specimen.

Acetylation of 2-p-*Nitrophenylpyrrocoline.*—A solution of the nitro-compound (2 g.) and fused sodium acetate (2 g.) was refluxed for 24 hrs. in acetic anhydride (80 c.c.), and the solvent removed in a vacuum. From the residue there was obtained, by chromatography on alumina, 3-*acetyl*-2-p-*nitrophenylpyrrocoline*, yellow needles, m. p. 190·5—191°, after crystallisation from methyl cyanide. The nitro-compound can be sublimed at 150°/0·001 mm. without change in m. p. (Found : C, 68·7; H, 4·5; N, 10·2. $C_{16}H_{12}O_3N_2$ requires C, 68·6; H, 4·3; N, 10·0%).

1-*Nitro*-2-p-*nitrophenylpyrrocoline.*—(*a*) Nitric acid (0·35 c.c.) was added dropwise to an ice-cold, stirred solution of 2-phenylpyrrocoline (0·5 g.) in concentrated sulphuric acid (1·5 c.c.), and the reaction mixture poured on ice. The precipitated material, after recrystallisation from methyl cyanide and then acetone (charcoal), yielded 1-nitro-2-nitrophenylpyrrocoline (0·33 g.; 45%), yellow needles, m. p. 235—236° alone and on admixture with an authentic specimen described below (Found : N, 14·4%).

(*b*) In a similar manner nitration of 2-*p*-nitrophenylpyrrocoline (0·2 g.) in sulphuric acid (2 c.c.) at 0° with nitric acid (0·07 c.c.) yielded an identical product (0·08 g.), m. p. 235—236°.

2-*Phenylpyrrocoline Nitrate.*—On addition of nitric acid (0·08 c.c.) to a solution of 2-phenylpyrrocoline in acetic acid (6 c.c.) containing nitric acid (0·08 c.c.) monoclinic needles separated; these melted at 134° with vigorous decomposition (Found, after drying at room temp. in a vacuum : C, 54·5; H, 4·8; N, 13·0. $C_{14}H_{11}N,1{\cdot}8HNO_3$ requires C, 54·8; H, 4·2; N, 12·8%). Recrystallisation from ethyl acetate results in a gradual fall in the content of nitric acid, the free base being obtained eventually. The nitrate was prepared in larger quantity as follows. 2-Phenylpyrrocoline (10 g.) was triturated with a mixture of concentrated nitric acid (10 c.c.) and glacial acetic acid (100 c.c.), and the flocculent mass removed,

washed with successive small portions of acetic acid, and well pressed. The product, m. p. 134° (decomp.), was identical with that described above.

The nitrate was added portionwise to stirred concentrated sulphuric acid (30 c.c.) kept below 10°, the clear yellow syrup poured on ice, and the solid product immediately filtered off, washed thoroughly with water, and dried. The dark orange solid (11·5 g.), crystallised thrice from hot methyl cyanide, yielded 1-*nitro*-2-p-*nitrophenylpyrrocoline*, yellow needles, m. p. 235·5—236°. A portion was sublimed at 180°/0·005 mm. for analysis (Found: C, 59·6; H, 3·3; N, 14·7. $C_{14}H_9O_4N_3$ requires C, 59·4; H, 3·2; N, 14·8%). Examination of the original methyl cyanide mother-liquor yielded no tractable product other than an additional quantity (1·1 g.) of the dinitro-compound, bringing the total yield to 47·5%.

Oxidation of 1-nitro-2-*p*-nitrophenylpyrrocoline (1·4 g.) with perhydrol (15 c.c.) and acetic acid (10 c.c.) yielded α-picolinic acid *N*-oxide (0·2 g.) and *p*-nitrobenzoic acid (0·4 g.).

Nitration of 3-*Acetyl*-2-*phenylpyrrocoline.*—(a) *With* 1 *mol. of nitric acid.* A solution of the acetyl compound (30 g.) in concentrated sulphuric acid (140 c.c.) was stirred and kept at −10° to −5° during the dropwise addition of nitric acid (8·3 c.c.) and then added slowly to vigorously stirred ice-water (1000 c.c.). The precipitated greenish-yellow solid rapidly darkened during this operation and the subsequent filtration and washing with water (1000 c.c.). The crude solid (21·5 g.), dissolved in the minimum volume of cold acetone, was filtered down a column (2 × 10 cm.) of alumina, which was washed with fresh acetone until the eluate became pale. The contents of the multi-coloured chromatograms proved intractable. The residue (13 g.) after evaporation of the acetone eluates was dissolved in the minimum quantity of benzene and filtered down a fresh column (3 × 30 cm.) of alumina. The chromatogram was developed with fresh benzene, giving a yellow and a green chromatogram with a brown zone at the top. From the green chromatogram benzene extracted a fraction (3·2 g.) which, after crystallisation from methyl cyanide (charcoal) and then chloroform–ligroin, yielded 1 : 3-*dinitro*-2-p-*nitrophenylpyrrocoline* (2·3 g.), a yellow micro-crystalline powder, m. p. 232—233° (decomp.) (Found: C, 51·5; H, 2·2; N, 17·1. $C_{14}H_8O_6N_4$ requires C, 51·2; H, 2·4; N, 17·0%).

The yellow chromatogram yielded, after systematic fractional crystallisation: (i) 1 : 3-dinitro-2-*p*-nitrophenylpyrrocoline (1·2 g.); (ii) 3-*nitro*-2-p-*nitrophenylpyrrocoline* (2·8 g.), yellow monoclinic needles from chloroform–ligroin, m. p. 211° (largely depressed when mixed with the 1-nitro-isomeride, m. p. 235·5—236°) (Found: N, 14·6%); (iii) 3-acetyl-2-*p*-nitrophenylpyrrocoline (1·6 g.), yellow needles from methyl cyanide, m. p. 190·5—191° alone and when mixed with the compound obtained by acetylation of 2-*p*-nitrophenylpyrrocoline (Found: N, 10·4%); (iv) 1-nitro-3-acetyl-2-*p*-nitrophenylpyrrocoline, yellow nodules (0·6 g.) from chloroform–ligroin, m. p. 173—175° alone or mixed with an authentic specimen.

(b) *With* 2 *mols. of nitric acid.* Nitration of 3-acetyl-2-phenylpyrrocoline (30 g.) with 2 mols. of nitric acid (16·5 c.c.) was carried out essentially as in (a). The dried product (30 g.) in acetone was filtered down a column of alumina and the eluate concentrated to yield a mixture of nitro-compounds (26 g.), from which by crystallisation from methyl cyanide (700 c.c.) a crop of crystals (9·1 g.) was obtained. This by crystallisation from chloroform was separated into 1 : 3-dinitro-2-*p*-nitrophenylpyrrocoline (3·9 g.), m. p. 232—233° (decomp.) alone or when admixed with the compound isolated from preparation (a) (Found: C, 51·4; H, 2·7; N, 16·8%), and 3-nitro-2-*p*-nitrophenylpyrrocoline, yellow needles (3·3 g.) m. p. 211°, from chloroform–ligroin (Found: C, 59·5; H, 3·5; N, 14·6%). The methyl cyanide mother-liquor (700 c.c.) was concentrated in a vacuum, and the residue fractionally crystallised from chloroform–ligroin to remove a trace of the less soluble 1 : 3-dinitro-2-*p*-nitrophenylpyrrocoline and to yield 1-*nitro*-3-*acetyl*-2-p-*nitrophenylpyrrocoline* (8·35 g.), which separated in yellow needles, m. p. 173—175° (Found: C, 59·0; H, 3·6; N, 12·9. $C_{16}H_{11}O_5N_3$ requires C, 59·1; H, 3·4; N, 12·9%). From the various filtrates, there was isolated, by chromatography on alumina, 3-acetyl-2-*p*-nitrophenylpyrrocoline (50 mg.), yellow needles, m. p. 190·5—191° alone and admixed with an authentic specimen.

Oxidation of 1-nitro-3-acetyl-, 3-nitro- and 1 : 3-dinitro-2-*p*-nitrophenylpyrrocoline in acetic acid with perhydrol gave, in each case, α-picolinic acid *N*-oxide and *p*-nitrobenzoic acid.

BATTERSEA POLYTECHNIC, S.W. 11.
GLAXO LABORATORIES LTD., GREENFORD.

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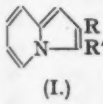
239. *The Chemistry of the Pyrrocolines. Part IV. Reduction of Acyl Derivatives.*

By E. T. BORROWS, D. O. HOLLAND, and J. KENYON.

The position of the acetyl group in 3-acetyl-2-methyl- and -2-phenyl-pyrrocoline has been determined by the reduction of these derivatives to 2-*methyl*- and 2-*phenyl*-3-*ethylpyrrocoline* respectively, and comparison with the same compounds prepared by direct synthesis. The catalytic reduction of these compounds has also been studied. The position of the benzoyl group in 3-benzoyl-2-phenylpyrrocoline has been established in a similar manner.

UNSUCCESSFUL attempts to confirm the position of the acetyl group in 3-acetyl-2-methyl- and -2-phenyl-pyrrocoline (I, R = Me or Ph; R′ = Ac), either by direct synthesis or *via* the corresponding 3-carboxylic esters, have already been recorded (Part I). The desirability of establishing this position became apparent in the work on the nitrosation and nitration of the pyrrocoline ring system (Parts II and III), since the orientation of the nuclear substituents in the compounds was largely dependent on the position of the acetyl group. The possibility of solving this problem by means of the corresponding 3-ethylpyrrocolines (I; R = Me or Ph, R′ = Et) was therefore examined and the direct synthesis of these compounds in good yield from α-picoline and 3-*bromo*-2-*pentanone* and α-bromobutyrophenone respectively is now described, using the method of Tschitschibabin (*Ber.*, 1927, **60**, 1607). Ochiai and Tsuda (*Ber.*, 1934, **67**, 1011) have prepared 2 : 3-dimethylpyrrocoline in a similar fashion, using 3-bromobutanone, and it would appear therefore that Tschitschibabin's method is generally applicable for the synthesis of 2 : 3-dialkyl- or -aryl-substituted pyrrocolines. Only a very small yield (*ca.* 1%) of 2-*methyl*-3-*ethylpyrrocoline* was



(I.)

obtained when the 3-chloro-ketone was used, compared with 75% in the case of the bromo-ketone, indicating the advisability of using bromo-ketones in this type of reaction.

In common with all other known alkyl- and aryl-pyrrocolines, 2-methyl-3-ethyl- and 2-*phenyl*-3-*ethyl-pyrrocoline* exhibit in solution a bluish-violet fluorescence and give positive reactions in the pine-splinter test (red) and a coloured melt on fusion with oxalic acid (2-methyl, green; 2-phenyl, blue). The 2-methyl-3-ethyl derivative is even more unstable to air and light than is 2-methylpyrrocoline, while the 2-phenyl derivative, a comparatively low-melting solid (m. p. 94°), is quite stable, as are other known arylpyrrocolines.

Attention was then directed to the possibility of reducing the acetylpyrrocolines to the corresponding ethyl derivatives. Tschitschibabin and Stepanow (*Ber.*, 1929, **62**, 1068) record that the action of ethylmagnesium bromide on 3-acetyl-2-methylpyrrocoline gives rise to the 2-methyl-3-ethyl compound, reduction with aluminium amalgam in moist ether apparently giving the same compound. The product they obtained, however, was later shown to be 2-methylpyrrocoline by Kondo and Osawa (*J. Pharm. Soc. Japan*, 1936, **56**, 73; *Chem. Zentr.*, 1936, **107**, ii, 2910). Since the acetyl groups in these pyrrocolines are so readily removed by hydrolysis with mineral acid (Part I), it was clear that a normal Clemmensen reduction would be useless, but the possibility of using dry alcohol saturated with dry hydrogen chloride with the amalgamated zinc was examined (cf. Adams, Cain, and Baker, *J. Amer. Chem. Soc.*, 1940, **62**, 2201; Schneider and Spielman, *J. Biol. Chem.*, 1942, **142**, 345). This reagent, however, converted 3-acetyl-2-methylpyrrocoline almost exclusively into 2-methylpyrrocoline. A control experiment, without zinc, showed that alcoholysis was responsible for this result, a 92% conversion into 2-methylpyrrocoline being obtained after refluxing for 15 hrs.

Scholtz (*Ber.*, 1912, **45**, 734) has already shown the pyrrocoline nucleus to be unaffected by zinc and acetic acid, and we therefore employed glacial acetic acid as the medium for the Clemmensen reduction, passing a slow stream of dry hydrogen chloride through the reaction mixture. The product obtained, a yellow, unstable, fluorescent oil, distilled over a wide range, even on careful fractionation, and was an obvious mixture. It was finally separated into two main products by fractional crystallisation of the crude picrate and the identity of one of these as 2-methyl-3-ethylpyrrocoline was established through its *chloroplatinate* and suspected picrate: the other product was probably 2-methyl-3-α-hydroxyethylpyrrocoline (II) since it yielded a *phenylurethane*.

Although these 3-acetyl-pyrrocolines are unreactive towards phenylhydrazine, the preparation of 2 : 4-dinitrophenylhydrazones (Part I) indicated that Kon's modification (*J.*, 1940, 1325) of the Kishner–Wolff method might be effective. This proved to be the case, and 2-phenyl-3-ethylpyrrocoline was obtained by this method, although a larger proportion of 2-phenylpyrrocoline was also formed during the reaction. The introduction of ethyl groups into the pyrrole nucleus by heating with alcoholic sodium ethoxide is well known (Fischer and Bartholomäus, *Z. physiol. Chem.*, 1912, **80**, 7, 15), and Knorr and Hess (*Ber.*, 1912, **45**, 2634) have replaced the acetyl group in 3-acetyl-2 : 4 : 5-trimethylpyrrole by an ethyl group in the same way. It was necessary, therefore, in view of the isolation of 2-phenylpyrrocoline, to establish that the reaction had not proceeded by deacetylation of the acetyl derivative, followed by the introduction of an ethyl group. 2-Phenylpyrrocoline was recovered unchanged after being heated in a sealed tube with alcoholic sodium ethoxide, and the 3-acetyl derivative, under the same conditions, was converted mainly into 2-phenylpyrrocoline, together with a comparatively small quantity of an unidentified unstable yellow oil.

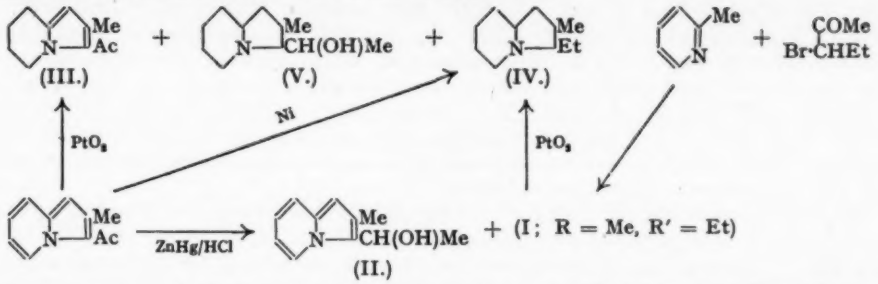
The isolation of 2-phenyl-3-ethylpyrrocoline from the original reaction mixture may, therefore, be safely assumed to be due to direct reduction of the acetyl group, *via* the hydrazone, thus establishing the position of this in the initial material.

Attempts to prepare a thioacetal derivative of the acetyl compounds, with a view to employing the recent method of Wolfrom and Karabinos (*J. Amer. Chem. Soc.*, 1944, **66**, 909) for converting carbonyl into methylene groups, were unsuccessful.

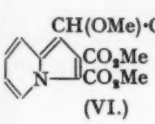
The Kishner–Wolff method was also successfully used for the reduction of 3-benzoyl-2-phenylpyrrocoline (Part I), 2-*phenyl*-3-*benzylpyrrocoline* being isolated in 26% yield, together with a 49% yield of 2-phenylpyrrocoline. The same compound was obtained (25% yield) by direct synthesis from α-picoline and α-bromo-α-benzylacetophenone, thus establishing the position of the benzoyl group in the original compound. The hydrochloride of this pyrrocoline was an oil, and the *picrate*, m. p. 112·5—113·5°, also tended to form an oil unless carefully crystallised.

The possibility of employing catalytic reduction for the conversion of the acetyl into an ethyl group was also investigated, but it soon became clear that selective reduction of this group without affecting the nucleus was impossible. Signaigo and Adkins (*J. Amer. Chem. Soc.*, 1936, **58**, 709) found that acylpyrroles such as 3-acetylpyrrole could be reduced to the corresponding ethylpyrrole when Raney nickel or copper chromite was used as catalyst. We find that 3-acetyl-2-phenylpyrrocoline is reduced to a tetrahydro-compound, probably 3-*acetyl*-2-*phenyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline* (X) in the presence of Raney nickel, even at room temperature and pressure. A similar *compound* (III) is obtained as the main product when 3-acetyl-2-methylpyrrocoline is reduced at room temperature and pressure using Adams's catalyst, although Ochiai and Kobayashi (*J. Pharm. Soc. Japan*, 1936, **56**, 376; *Chem. Abs.*, 1936, **30**, 6364; *Chem. Zentr.*, 1936, **107**, ii, 1938) record that 2-methyl-3-ethyl- (IV) and 2-methyl-3-α-hydroxyethyl-octahydropyrrocoline (V) were produced under similar conditions. We obtained only small quantities of two products believed to be identical with these two compounds, however, and it seems probable that the Japanese workers added the catalyst portionwise to their reaction mixture.

The products obtained from 3-acetyl-2-methylpyrrocoline in this reduction, the Clemmensen reduction above, and those to be mentioned later are given in the following scheme :



Both tetrahydro-compounds are low-melting solids, and give slowly-developing colours in the pine-splinter test (2-methyl, red; 2-phenyl, purple), but fusion with oxalic acid gives colourless melts. Failure to form urethanes, and the preparation of dinitrophenylhydrazones, indicated that the acetyl group had not been reduced. Since the original 3-acetylpyrrocolines gave coloured (green) melts with oxalic acid, it appeared probable that the 6-membered ring had been reduced in these compounds, a conclusion supported by the fact that on heating with mineral acid the 2-phenyl analogue (X) readily lost the acetyl group to give 2-*phenyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline*, m. p. 76·5—77° (XI); this compound regenerates the acetyl derivative on heating with acetic anhydride and fused sodium acetate. The apparent reduction of the 6-membered ring of the pyrrocoline nucleus, by the action of sodium on an alcoholic solution of the parent base, was noted by Scholtz (*loc. cit.*). Two atoms of hydrogen were introduced in this way to produce an unstable oil which gave a positive result in the pine-splinter test but a colourless melt with oxalic acid. Scholtz considered that the compound was α-butadienylpyrrole, but it seems more likely that it was a dihydropyrrocoline. It may be noted in this connection, however, that Diels and Meyer (*Annalen*, 1934, **513**, 129) considered that when the tricarboxylic ester (VI) was hydrogenated with platinum oxide as catalyst, the 5-membered ring was reduced, since the acids obtained on hydrolysis before and after hydrogenation gave different anhydrides on treatment with acetic anhydride, a difference which was explained by *cis*- and *trans*-isomerism, assuming the 5-membered ring to have been reduced.

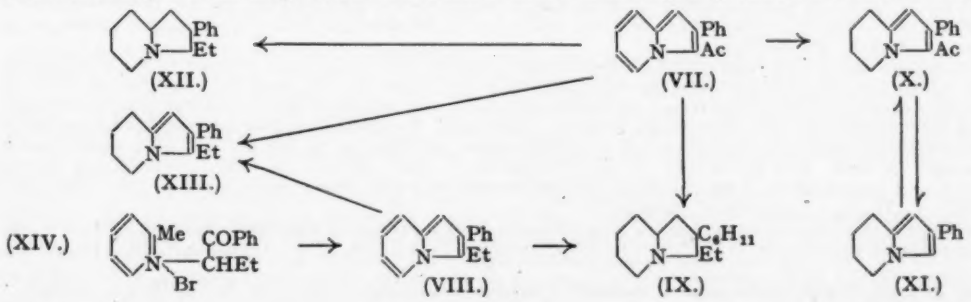


(VI.)

Using copper chromite as catalyst, the main product when 3-acetyl-2-phenylpyrrocoline was hydrogenated at 170—175° for 1·5 hrs. under 150 atm. was a white solid, m. p. 100—101°, believed to be 2-*phenyl*-3-*ethyl*-5 : 6 : 7 : 8-*tetrahydropyrrocoline* (XIII). This same compound, obtained in good yield when 2-phenyl-3-ethylpyrrocoline was hydrogenated at room temperature and pressure in the presence of Raney nickel, gave a purple-red colour in the pine-splinter test and a colourless oxalic acid melt, whilst its solutions in organic solvents exhibited a violet fluorescence. Under more vigorous conditions increasing amounts of 2-*phenyl*-3-*ethyl*-*octahydropyrrocoline* (XII) were obtained with both Raney nickel and copper chromite. This compound, a high boiling oil, was at first considered to be 2-*cyclo*hexyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline, both from the analytical data and from its red-purple coloration in the pine-splinter test. Its absorption spectrum, however, which was very low ($\lambda_{max.}$ 2980 A., ε 55, with general absorption below 2710 A.), was not in harmony with this structure and showed little resemblance to, *e.g.*, that of 2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline.

That the product was, in fact, contaminated with a " pyrrole " impurity was shown by treatment of the crude base in ligroin with dry hydrogen chloride to yield as the major product 2-*phenyl*-3-*ethyloctahydropyrrocoline hydrochloride*, which was isolated in two isomeric forms, m. p. 199—200° and m. p. 231—232°. The free base from both of these salts gave a negative pine-splinter test and by oxidation with potassium permanganate yielded benzoic acid.

With Raney nickel as catalyst it was possible, finally, to obtain the fully-reduced 2-cyclo*hexyl*-3-*ethyl*-*octahydropyrrocoline* (IX) from both (*a*) 3-acetyl-2-phenylpyrrocoline and also (*b*) 2-phenyl-3-ethylpyrrocoline, the reduction being considerably slower in the latter case. The various products are shown in the scheme :



The *hydrochlorides* and the hydrobromides prepared from both specimens (*a*) and (*b*) of the fully-reduced base possessed the same m. p.'s, which were not depressed on admixture. The *methiodides*, however, were quite different : that from the base (*a*) had m. p. 201—202°, and that from (*b*) m. p. 188—189°. The m. p. of mixtures of these two solids was in all cases 201—202°, unless only a very small proportion of the higher-melting derivative was present, whereupon the mixtures melted at 197°. All attempts at interconversion of these two forms were unsuccessful, and when the higher-melting derivative was fused (1—2 mins.) a third form was produced, m. p. 208—209°, after crystallisation from acetone–ligroin. Careful fractional crystallisation of the crude methiodides from each of the bases showed that each was uncontaminated with the other (synthetic mixtures were readily separated from acetone–ligroin), but a small quantity of a fourth form, m. p. 177—178°, was isolated in this way from the crude methiodide of (*b*).

A similar phenomenon was observed with the methiodide of 2-methyl-3-ethyloctahydropyrrocoline. Ochiai and Kobayashi (*loc. cit.*), who prepared this derivative, give the m. p. as 197°. By reducing the 3-acetyl-2-methyl compound, following their method (see above), and converting the appropriate fraction into its methiodide, a rather deliquescent solid was obtained from which it was only possible to isolate very small quantities of two solids, m. p. 218—220°, and m. p. 196—198°, which could not be completely purified. It is interesting to note that the fraction corresponding to 2-methyl-3-α-hydroxyethyloctahydropyrrocoline gave a phenylurethane, m. p. 137° (Ochiai and Kobayashi, m. p. 137°) which was readily purified. 2-Methyl-3-ethyl-octahydropyrrocoline (*c*) prepared from the 3-acetyl compound by hydrogenation at high temperature and pressure using Raney nickel as catalyst, gave a methiodide which was not deliquescent in the crude state and was more readily purified, m. p. 197—198°. The methiodide of the fully-reduced base (*d*) obtained by the reduction of 2-methyl-3-ethylpyrrocoline using Adams's catalyst (following Ochiai and Tsuda, *loc. cit.*), however, had m. p. 229—229·5°. The m. p.s of mixtures of these two forms behaved similarly to those described above for the corresponding 2-phenyl analogue. The perchlorates, hydriodides, and hydrobromides prepared from both specimens (*c*) and (*d*) possessed the same m. p.s, which were not depressed on admixture. Clemo and Ramage (*J.*, 1932, 2969) have recorded the isolation of two picrates of octahydropyrrocoline which behaved similarly to the methiodides described above.

Experimental.

All m. p.'s are uncorrected.

3-Chloro-2-pentanone.—Freshly distilled sulphuryl chloride (43 c.c.) was added dropwise during 90 mins. to stirred 2-pentanone (43 g.) at 0—5°, and the mixture slowly heated on a steam-bath for 30 mins. The cooled liquid was diluted with ether, washed with water until neutral (Congo-red), dried, and distilled, the fraction, b. p. 124—140°, being collected (22·2 g.; 36·7%). On redistillation, the principal fraction had b. p. 36—38°/12 mm.

3-Bromo-2-pentanone.—No reference to this *compound* being found in the literature, we have prepared it essentially by the method used for bromoacetone (*Org. Synth.*, Coll. Vol. II, 88). Bromine (14·9 c.c.) was added dropwise to a stirred solution of 2-pentanone (25 g.) in a mixture of acetic acid (100 c.c.) and water (60 c.c.) at 65—70°, at such a rate that decolorisation was almost immediate (40 mins.). Absorption was rapid, and the reaction mixture maintained itself at 65° without external heating. The cooled mixture was poured into water (500 c.c.), neutralised with sodium carbonate (Congo-red), the liberated heavy lachrymatory oil separated, and the aqueous layer extracted twice with chloroform. The combined oil and extracts were washed with sodium carbonate solution, then with water and dried. The bromoketone was fractionally distilled through a Vigreux column, and the main bulk collected at 57—59°/18 mm. as a colourless, mobile, lachrymatory liquid (25·2 g.; 52·5%). A portion was analysed after refractionation (b. p. 53°/14 mm.) (Found : Br, 48·8. C_5H_9OBr requires Br, 48·5%); $n_D^{20°}$ 1·4629.

2-Methyl-3-ethylpyrrocoline.—A mixture of 3-bromo-2-pentanone (37·1 g.) and α-picoline (22·5 c.c.) was heated on a steam-bath for 15 hrs., and the resulting dark-brown gum shaken with water, the residual oily material being removed with chloroform. The aqueous layer was extracted with chloroform and mixed with sodium bicarbonate until effervescence ceased, and the liberated α-picoline extracted with ether. Additional bicarbonate (30 g.) was then added, the mixture heated on the steam-bath for 3 hrs., and the liberated *2-methyl-3-ethylpyrrocoline* removed in a current of steam as a heavy pale yellow oil. Distilled in a vacuum, it had b. p. 124°/15 mm. (27·1 g.; 75%) (Found : C, 83·0; H, 8·2; N, 9·0. $C_{11}H_{13}N$ requires C, 83·0; H, 8·2; N, 8·8%); $n_D^{20°}$ 1·5968. Its *chloroplatinate*, a buff-coloured powder, had m. p. 174° (decomp.) (Found : C, 36·5; H, 3·7; N, 4·3; Pt, 27·6. $C_{22}H_{26}N_2PtCl_6$ requires C, 36·3; H, 3·9; N, 3·9; Pt, 26·8%).

3-Pentan-2-onyl-α-picolinium chloroplatinate was obtained as a yellowish-buff powder, m. p. 225° (decomp.), from a portion of the aqueous solution after removal of α-picoline (as above), acidification with hydrochloric acid, and clarification with charcoal (Found : N, 4·0; Pt, 25·3. $C_{22}H_{32}O_2N_2Cl_6Pt$ requires N, 3·7; Pt, 25·6%).

Reaction of 3-Chloro-2-pentanone with α-Picoline.—A mixture of the ketone (7·9 g.) and α-picoline (6·6 c.c.) was heated on a steam-bath for 20 hrs., and the resulting dark syrup worked up as described above. The heavy yellow oil (0·13 g.) obtained possessed an odour similar to that of 2-methylpyrrocoline, and gave a red colour in the pine-splinter test and a green melt with oxalic acid. It was not further identified as 2-methyl-3-ethylpyrrocoline, but the chloroplatinate of the quaternary compound before ring closure was prepared and found to be identical with that described above, m. p. 220° (decomp.) (Found : N, 3·3; Pt, 25·9%).

2-Phenyl-3-ethylpyrrocoline.—A mixture of α-bromobutyrophenone (12·2 g.) and α-picoline (5 g.) was heated on a steam-bath for 3 hrs., the resulting brown syrup extracted with hot water (50 c.c.), and the insoluble oil removed with ether. The clarified aqueous solution was mixed with sodium hydrogen carbonate (30 g.), the liberated α-picoline extracted with ether, and the aqueous solution refluxed for 90 mins. The dark, fluorescent oil that separated solidified on cooling and was crystallised twice from alcohol (charcoal) as thin rhombic platelets, m. p. 94° (6·6 g.; 58% overall yield from α-picoline) (Found : C, 86·8; H, 7·1; N, 6·6. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%). Its *picrate*, prepared in alcoholic solution and recrystallised from the same solvent, formed greenish-yellow needles, m. p. 157—158° (decomp.) (Found, N, 12·1. $C_{22}H_{18}O_7N_4$ requires N, 12·5%).

α-Butyrophenonyl-α'-picolinium chloroplatinate was obtained, from a portion of the clarified aqueous solution described above, as a buff-coloured precipitate, m. p. 178° (decomp.) (Found : N, 3·2; Pt, 21·5. $C_{32}H_{36}O_2N_2PtCl_6$ requires N, 3·2; Pt, 22·0%).

Reduction of 3-Acetyl-2-methylpyrrocoline (Clemmensen Method).—Amalgamated zinc wool (100 g.), washed several times with alcohol and finally with acetic acid, was mixed with a solution of the acetyl compound (20 g.) in anhydrous

acetic acid (250 c.c.), and the whole heated under reflux for 7 hrs., whilst a slow stream of hydrogen chloride was passed in. The colourless solution, separated from the zinc, was rendered strongly alkaline with sodium hydroxide, and the liberated oil removed in a current of steam (12·3 g.). This distilled at 104—128°/12 mm., giving two main fractions: (i) b. p. 104—107° (2·32 g.), (ii) b. p. 120—125° (2·66 g.). By combination with picric acid and fractional crystallisation of the resulting salts from acetone–ether (i) yielded as the main product, *2-methyl-3-(α-hydroxyethyl)pyrrocoline picrate*, pale yellow platelets from methyl alcohol, m. p. 141·5—142° (Found: C, 50·4; H, 4·4; N, 14·2. $C_{17}H_{16}O_8N_4$ requires C, 50·5; H, 4·0; N, 13·9%). By reaction with phenyl *iso*cyanate, the corresponding *urethane* was obtained, needles from alcohol, m. p. 142—142·5° (Found: N, 9·2. $C_{18}H_{18}O_2N_2$ requires N, 9·5%). Fraction (ii) yielded, as the main product, a picrate as greenish-yellow needles from alcohol, m. p. 124° (decomp.), which was not depressed on admixture with the picrate, m. p. 124° (decomp.), prepared in a similar way from 2-methyl-3-ethylpyrrocoline. Good analyses could not be obtained with either specimen of this derivative (N values varied from 12·5 to 13·6%), but it was possible to convert it into a chloroplatinate, m. p. 174° (decomp.), not depressed on admixture with 2-methyl-3-ethylpyrrocoline chloroplatinate.

Examination in the same way of the other fractions from the distillation showed that they were mixtures of the two products described above.

Reduction of 3-Acetyl-2-phenylpyrrocoline (Kishner–Wolff Method).—The pyrrocoline (7 g.), hydrazine hydrate (30 c.c. of 85%), and a solution of sodium (14 g.) in absolute alcohol (280 c.c.) were heated together in a steel autoclave at 180° for 22 hrs. From the cooled contents of the autoclave, 2-phenylpyrrocoline (2·6 g.; identified by m. p. and conversion into picrate) was removed by filtration. The filtrate, freed from alcohol, diluted with water, and extracted with ether yielded 2-phenyl-3-ethylpyrrocoline, rhombic platelets (2·3 g., 35% yield) from ligroin; m. p. 94° alone and mixed with an authentic specimen (Found: C, 87·0; H, 6·7; N, 6·0%). Its picrate had m. p. 157—158° (decomp.) alone and mixed.

2-Phenyl-3-benzylpyrrocoline.—Benzylideneacetophenone (20·8 g.) was reduced (*Org. Synth.*, Coll. Vol. I, 95) to benzylacetophenone (19·1 g.). Bromination of the latter (Kohler and Kimball, *J. Amer. Chem. Soc.*, 1934, **56**, 730) gave the required α-bromo-α-benzylacetophenone in good yield. A mixture of this bromo-ketone (10·2 g.) and α-picoline (3·8 g.) was heated on the steam-bath for 30 mins.; after 3 days the resulting thick brown oil was extracted several times with hot water, and the aqueous solution clarified by extraction with ether and shaking with charcoal. To the major portion (120 c.c.) sodium hydrogen carbonate (12 g.) was added, the mixture heated under reflux for 1 hr., and the liberated oil extracted with ether. The extract, after two recrystsllisations from alcohol, gave *2-phenyl-3-benzylpyrrocoline* (2·54 g.), colourless needles, m. p. 100—101° (Found: C, 88·9; H, 6·2; N, 5·0. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0; N, 5·0%). Its *picrate*, prepared in alcoholic solution and recrystallised from *iso*propyl alcohol, forms yellow irregular rhombs, m. p. 112·5—113·5° (decomp.) (Found: C, 63·7; H, 4·4; N, 10·6. $C_{27}H_{20}O_7N_4$ requires C, 63·3; H, 3·9; N, 10·9%).

N-*(α-Benzylphenacyl)-α′-picolinium chloroplatinate* separated, from a portion of the clarified aqueous solution described above, as a buff-coloured powder, m. p. 142—143° (decomp.) (Found: N, 2·7; Pt, 19·4. $C_{42}H_{40}O_2N_2Cl_6Pt$, requires N, 2·9; Pt, 19·3%).

Reduction of 3-Benzoyl-2-phenylpyrrocoline (Kishner–Wolff Method).—A mixture of the pyrrocoline (7 g.), hydrazine hydrate (30 c.c. of 95%), and a solution of sodium (4 g.) in absolute alcohol (150 c.c.) was heated for 20 hrs. at 170° in a steel autoclave. Filtration of the cooled product removed a crystalline solid (4·18 g.) which, after purification by extraction with hot alcohol (30 c.c.), was identified as 2-phenylpyrrocoline (2·2 g.). From the alcoholic extract, needles were obtained on cooling, separated from contaminating 2-phenylpyrrocoline by solution in dry benzene (5 c.c.). The original filtrate, after concentration in a vacuum, dilution with water and extraction of the insoluble oil into ether, yielded a crude solid which was mixed with the benzene extract described above. From this mixture 2-phenyl-3-benzylpyrrocoline was obtained, (1·75 g.), needles from alcohol, m. p. 100—101° alone or when mixed with the material prepared by the method described above (Found: C, 88·8; H, 6·2; N, 4·8%). The picrate, m. p. 112·5—113·5° (decomp.), likewise proved to be identical with that of 2-phenyl-3-benzylpyrrocoline described above (Found: N, 11·2%).

Reduction of 3-Acetyl-2-methylpyrrocoline (by Use of Platinum Oxide).—A solution of the acetyl compound (9 g.) in A.R. glacial acetic acid (15 c.c.) was hydrogenated in the presence of Adams's catalyst (0·5 g.) at room temperature and pressure. Reaction ceased after 15 hrs., when 5·1 l. of hydrogen had been absorbed (7·7 l. required for complete reduction). The solution on dilution with water deposited white, greasy platelets of crude *3-acetyl-2-methyl-5 : 6 : 7 : 8-tetrahydropyrrocoline*, m. p. 71—73°. The solid was removed, and the filtrate neutralised with sodium hydroxide, another 0·34 g. of the same compound separating (4·2 g. total). It recrystallised from dilute alcohol (charcoal) as colourless needles, m. p. 74—74·5° (Found: C, 74·2; H, 8·2; N, 8·3. $C_{11}H_{15}ON$ requires C, 74·6; H, 8·5; N, 7·9%).

The neutral filtrate was rendered strongly alkaline and shaken with ether to extract a brown oil (4·2 g.). This was fractionally distilled to give two clear-cut fractions: (i) b. p. 80—85°/11 mm. (1·43 g.), (ii) b. p. 106—110°/11 mm. (1·93 g.), leaving a brown residue. Reaction of fraction (i) with methyl iodide yielded a brown oil, obtained as a pale yellow rather deliquescent solid on rubbing with dry ethyl acetate. Fractional crystallisation of this from alcohol–ethyl acetate gave a very small quantity of an amorphous powder, m. p. 218—220°, and tiny rhombic platelets, m. p. 196—198°, which liquefied rapidly in air. Fraction (ii) combined with phenyl *iso*cyanate to yield the phenylurethane of 2-methyl-3-(α-hydroxyethyl)octahydropyrrocoline, a microcrystalline powder, m. p. 136—137° (Found: C, 71·3; H, 8·8; N, 9·0. Calc. for $C_{18}H_{24}O_2N_2$: C, 71·5; H, 8·6; N, 9·3%).

The *benzylidene* derivative of 3-acetyl-2-methyl-5 : 6 : 7 : 8-tetrahydropyrrocoline, prepared from a solution of the acetyl derivative (2·0 g.), benzaldehyde (3·0 c.c.), and sodium hydroxide (4 c.c. of 2N) in alcohol (20 c.c.), was deposited after 3 days on scratching as yellow prisms; recrystallised from alcohol, m. p. 126—127° (Found: C, 80·9; H, 7·2; N, 5·5. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%); and the *2 : 4-dinitrophenylhydrazone*, purified by dissolving it in a large volume of hot ethyl acetate and concentration until solid began to separate, formed tiny, black, monoclinic prisms, appearing ruby-red under the microscope, m. p. 209—210° (Found: C, 57·4; H, 5·3; N, 19·7. $C_{17}H_{19}O_4N_5$ requires C, 57·1; H, 5·3; N, 19·6%). Attempts to prepare a phenylhydrazone of 3-acetyl-2-methyl-5 : 6 : 7 : 8-tetrahydropyrrocoline were unsuccessful.

3-Acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline : Reduction of 3-Acetyl-2-phenylpyrrocoline at Room Temperature (using Raney Nickel). Expt. I (*see Table*).—The hydrogen absorption, which ceased after 25 hrs., could not be induced to continue by addition of fresh catalyst. After removal of the catalyst, the solution was concentrated in a vacuum to give an almost colourless oil which by solution in hot ligroin (b. p. 40—60°) yielded *3-acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline*; needles, m. p. 81—82° (9·3 g.; 91%) (Found: C, 80·3; H, 7·0; N, 5·9. $C_{11}H_{17}ON$ requires C, 80·3; H, 7·1; N, 5·9%). Its *2 : 4-dinitrophenylhydrazone*, prepared in alcoholic solution and recrystallised from acetic acid, formed red needles, m. p. 228—229° (Found: N, 16·3. $C_{22}H_{21}O_4N_5$ requires N, 16·7%).

Hydrolysis of 3-Acetyl-2-phenyltetrahydropyrrocoline : Preparation of 2-Phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline.—Hydrolysis of this pyrrocoline (2 g.) proceeded readily at room temperature by solution in concentrated hydrochloric acid (5 c.c.) for 10 minutes. The solution was made alkaline, and the precipitated *tetrahydropyrrocoline* was filtered off, washed, with water, and dried in a vacuum (P_2O_5), being obtained as a pale pink solid, m. p. 74—77°. Purification proved difficult: it sublimed slowly at 70°/0·006 mm. to an almost white sublimate which rapidly became buff and then more slowly, on exposure to air, brown. Recrystallisation was not very satisfactory, and absolute ethyl alcohol alone proved useful, the compound being obtained from this solvent as yellow crystalline rods tinted with brown, m. p. 76·5—

Summary of result of hydrogenation of 3-acetyl-2-phenylpyrrocoline with Raney nickel and copper chromite as catalyst.

Expt.	Wt. of acetyl cpd. (g.).	Vol. of dioxan (c.c.).	Catalyst and wt.	H_2 press. at room temp. (atm.)	Temp.	Time (hrs.).	Products.*
I	10	60	Ni, 4 g.	1	15°	25	A (9·3 g.)
II	5	160	Ni, 5 g.	70	130	1	A (3 g.); C (1·5 g.)
III	10	250	Ni, 7·5 g.	85	125—135	1	A (4·6 g.); C (2·6 g.); B (0·54 g.)
IV	15	250	„	120	170—175	1·1	C (11·4 g.); 1·4 g. of oil, b. p. 160—180°/12 mm., not investigated
V	30	250	Ni, 10 g.	117	180	2·5	C (24·3 g.); two uninvestigated oils, b. p. 168°/12 mm. and 120—140°/0·25 mm.
VI	25	300	Ni, 10 g.	125	190	10·2	D (23·0 g.)
VII	10	200	$CuCrO_3$, 2 g.	150	170—175	1·5	C (4·28 g.); B (3·7 g.)
VIII	12	200	$CuCrO_3$, 2 g.	120	180—200	4	C (5·4 g.); B (2·5 g.)

* A = 3-Acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline; B = 2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline; C = 2-phenyl-3-ethyloctahydropyrrocoline; D = 2-*cyclo*hexyl-3-ethyloctahydropyrrocoline.

77·5° (Found : N, 7·2. $C_{14}H_{15}N$ requires N, 7·1%). An immediate deep purple colour was obtained in the pine-splint test. Its *picrate* separated from alcoholic solution as a red solid, unstable to prolonged heating in organic solvents, picric acid being set free. It was recrystallised from a warm mixture of alcohol and ligroin (b. p. 80—100°), forming fine red needles, m. p. 111·5—112·5° (Found : C, 56·1; H, 4·3; N, 13·4. $C_{20}H_{18}O_7N_4$ requires C, 56·3; H, 4·2; N, 13·1%).

Acetylation of 2-Phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline.—The tetrahydropyrrocoline (0·65 g.) was heated under reflux in acetic anhydide (8 c.c.) in the presence of fused sodium acetate (0·1 g.) for 2·25 hrs. The resulting almost black solution was concentrated under reduced pressure, and the residual oil shaken with water and ether. The ethereal solution, after being dried and concentrated left a residue which after being crystallised twice from ligroin gave 3-acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline (0·4 g.), m. p. 81—82° alone and when mixed with an authentic specimen. It yielded a dinitrophenylhydrazone, m. p. 228—229°, similarly not depressed by an authentic specimen.

2-Phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline.—(a) *By reduction of 3-acetyl-2-phenylpyrrocoline (with copper chromite). Expt.* VIII (*see Table*). Distillation of the resulting fluorescent oil gave two fractions, (i) b. p. 158—161°/12 mm. (5·4 g.), (ii) b. p. 198—204°/12 mm. Fraction (ii) yielded, on dissolving in hot *iso*propyl alcohol, *2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline* (2·5 g.) which after recrystallisation had m. p. 100—101° (Found : C, 85·4; H, 8·3; N, 6·1. $C_{16}H_{19}N$ requires C, 85·3; H, 8·4; N, 6·2%). A picrate could not be prepared, and the chloroplatinate, m. p. 115—120° (decomp.), could not be purified. It was best characterised by its U.V. absorption spectrum : $\lambda_{max.}$ 2780 A., ϵ 7700; λ min. 2660 A., ϵ 6960; inflexion 2400 A., ϵ 1100. Fraction (i) yielded a mixture of two hydrochlorides, m. p. 199—200° and 231—232°, identical with the hydrochlorides of 2-phenyl-3-ethyloctahydropyrrocoline described below. The hydrochloride obtained in larger amount, m. p. 231—232°, only was analysed (Found : C, 72·3; H, 9·1; N, 5·3%), and converted into the free *base* which had b. p. 156—157°/11 mm., $n_D^{20°}$ 1·5350 (Found : C, 83·6; H, 10·1; N, 6·2. $C_{16}H_{23}N$ requires C, 83·9; H, 10·0; N, 6·1%).

(b) *By reduction of 2-phenyl-3-ethylpyrrocoline (with Raney nickel).* A solution of the pyrrocoline (2·5 g.) in dioxan (25 c.c.) was hydrogenated at room temperature and pressure with Raney nickel (*ca.* 2 g.) as catalyst. Absorption of hydrogen ceased after 4·5 hrs. when 580 c.c. had been consumed (545 c.c. required for 2 mols. of hydrogen). The filtered solution was concentrated in a vacuum, and the residue crystallised from alcohol to yield 2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline, needles, m. p. 100—101° (2·32 g.; 92%), identical in all respects, including ultra-violet absorption spectrum, with the compound prepared in Expt. VIII. On oxidation with boiling permanganate it yielded benzoic acid.

2-Phenyl-3-ethyloctahydropyrrocoline.—Expt. III (*see Table*). The oily product obtained on concentration in a vacuum of the filtered dioxan solution from the hydrogenation gave 3-acetyl-2-phenyl-5 : 6 : 7 : 8-tetrahydropyrrocoline (4·6 g.), m. p. 81—82°, on crystallisation from ligroin. This product was identified in the usual manner. The ligroin filtrate yielded an oil (5·4 g.) which on distillation gave two fractions : (i) b. p. 158—162°/12 mm. (2·6 g.), (ii) b. p. 180—211°/12 mm. (2·2 g.). Fraction (ii), a yellow oil, deposited 2-phenyl-3-ethyl-5 : 6 : 7 : 8-tetrahydropyrrocoline (0·54 g.) from ligroin, needles, m. p. 100—101° alone and admixed with that from Expt. VIII (Found : C, 85·3; H, 8·4; N, 6·1%). Fraction (i) gave a positive reaction (reddish-purple) in the pine-splinter test and was freed from the " pyrrole " constituent by conversion into a mixture of hydrochlorides, m. p. 199—200° and 231—232°, which did not depress the m. p. of the 2-phenyl-3-ethyloctahydropyrrocoline hydrochlorides arising from Expt. V.

Expt. V (*see Table*). The product on fractional distillation gave a major fraction (24·3 g.), b. p. 156—158°/12 mm., $n_D^{20°}$ 1·5327 (Found : C, 82·7; H, 10·8; N, 5·8%). This oil, which gave a reddish-purple colour in the pine-splinter test, could not be purified by redistillation or chromatography and was finally freed from the " pyrrole " constituent by conversion into a mixture of two hydrochlorides which were separable by crystallisation. The acetone-insoluble *hydrochloride*, m. p. 231—232°, crystallised from methyl cyanide as colourless needles (Found, after drying in a vacuum at room temp. : C, 71·5; H, 8·7. $C_{16}H_{23}N,HCl,0·2H_2O$ requires C, 71·3; H, 9·1%. Found, after drying in a vacuum at 160° : C, 72·6; H, 9·2; N, 5·2; Cl, 13·5. $C_{16}H_{23}N,HCl$ requires C, 72·3; H, 9·0; N, 5·3; Cl, 13·4%). The acetone-soluble fraction on crystallisation from acetone–ligroin (b. p. 60—80°) yielded a *hydrochloride*, m. p. 199—200°, as a microcrystalline powder. (Found, after drying in a vacuum at room temp. : C, 71·5; H, 9·1%. Found, after drying in a vacuum at 110° : C, 72·0; H, 8·9; N, 5·4; Cl, 13·3%). Regeneration of 2-phenyl-3-ethyloctahydropyrrocoline from the first hydrochloride gave an oil, b. p. 156—157°/11 mm., $n_D^{20°}$ 1·5345 (Found : C, 84·3; H, 10·2; N, 5·7%). Oxidation of the oil with boiling permanganate in the presence of sodium hydrogen carbonate yielded benzoic acid.

Similarly the base derived from the hydrochloride, m. p. 199—200°, analysed satisfactorily (Found : C, 83·8; H, 10·0; N, 5·9%); $n_D^{20°}$ 1·5348.

Mixtures of the two hydrochlorides melted between 200° and 230° according to the proportions used; both gave a large depression of m. p. on admixture with 2-*cyclo*hexyl-3-ethyloctahydropyrrocoline hydrochloride (m. p. 219—220°) (below) and none of this was detected in the above reaction product.

2-cycloHexyl-3-ethyloctahydropyrrocoline.—(a) *By reduction of 3-acetyl-2-phenylpyrrocoline (with Raney nickel). Expt.* VI (*see Table*). The product on distillation gave *2-cyclohexyl-3-ethyloctahydropyrrocoline* as the sole fraction, b. p. 156—158°/12 mm., $n_D^{20°}$ 1·4988 (23·03 g.; 92%), a colourless oil which gave negative results in the pine-splinter and oxalic acid melt tests (Found : C, 81·7; H, 12·4; N, 6·2. $C_{16}H_{29}N$ requires C, 81·7; H, 12·3; N, 6·0%). The *hydrochloride*,

which was initially somewhat deliquescent, recrystallised from acetone as white needles, m. p. 219—220° (Found : C, 70·8; H, 11·0; N, 5·3; Cl, 13·0. $C_{16}H_{29}N$,HCl requires C, 70·7, H, 11·1; N, 5·2; Cl, 13·1%). The hydrobromide was prepared by evaporation of a solution of the base in hydrobromic acid (30%) under reduced pressure. The resulting oil crystallised from acetone–ether as a microcrystalline powder, m. p. 211—212°.

On admixture of the 2-*cyclo*hexyl-3-ethyloctahydropyrrocoline with an equal volume of methyl iodide a homogeneous solution resulted from which a yellow oil slowly separated to form a discrete upper layer, which gradually increased until the whole was once more homogeneous. This on trituration with ethyl acetate yielded the *methiodide* as a crystalline solid which recrystallised from acetone–ligroin (b. p. 60—80°) as white platelets, m. p. 201—202° (Found : C, 53·8; H, 8·4; N, 3·7; I, 33·5. $C_{17}H_{32}NI$ requires C, 54·1; H, 8·5; N, 3·7; I, 33·7%).

(b) *From* 2-*phenyl*-3-*ethylpyrrocoline*. A solution of this pyrrocoline (18 g.) in dioxan was hydrogenated in the presence of Raney nickel (10 g.) for 18 hrs. at 180°, with an initial hydrogen pressure of 123 atm. The oily product on distillation gave 2-*cyclo*hexyl-3-ethyloctahydropyrrocoline as a major fraction, b. p. 156—158°/12 mm., $n_D^{26°}$ 1·4989 (15·4 g.; 80%) (Found : C, 81·4; H, 12·2; N, 6·0%). The hydrochloride melted at 219—220° alone and on admixture with that from Expt. VI (Found : C, 70·8; H, 11·0; N, 4·9; Cl, 12·8%). Similarly the hydrobromide, m. p. 211—212°, was not depressed in m. p. on admixture with the specimen from Expt. VI.

When the methiodide was prepared essentially as in Expt. VI, it separated as a discrete lower layer from the initially homogeneous mixture. The white powder obtained on trituration of the yellow oil with ethyl acetate crystallised from acetone–ligroin (b. p. 60—80°) as white platelets, m. p. 188—189° (Found : C, 53·9; H, 8·5; N, 3·7; I, 34·1%).

2-*Methyl*-3-*ethyloctahydropyrrocoline*.—(a) *By reduction of* 3-*acetyl*-2-*methylpyrrocoline* (*using Raney nickel*). A solution of the acetyl compound (20 g.) in dioxan (200 c.c.) was hydrogenated at 180° for 5 hrs. at an initial pressure of 150 atm., Raney nickel (*ca.* 6 g.) being used as catalyst. The mobile ammoniacal liquid (14·3 g.) obtained after filtering and concentrating the solution was distilled, b. p. 79—86°/11 mm. It gradually discoloured on standing and deposited a heavy brown oil (Found : C, 79·2; H, 12·9; N, 8·0. $C_{11}H_{21}N$ requires C, 79·0; H, 12·6; N, 8·4%), $n_D^{20°}$ 1·4686. The pine-splint and oxalic acid melt tests were negative. Addition of methyl iodide to an ethereal solution of the base caused precipitation of the methiodide as a white powder; it recrystallised from alcohol–ethyl acetate as tiny needles, m. p. 197—198° (Found : C, 46·8; H, 7·4; N, 4·8; I, 40·9. Calc. for $C_{12}H_{24}NI$: C, 46·6; H, 7·8; N, 4·5; I, 41·1%). The perchlorate, precipitated as a pinkish powder on addition of 60% perchloric acid to a hydrochloric acid solution of the base, recrystallised from alcohol–ether as tiny colourless needles, m. p. 221·5—223° (lit. 220—221°) (Found : C, 49·3; H, 7·9. Calc. : C, 49·4; H, 8·2%). The hydrobromide was obtained by concentration in a vacuum of a solution of the base in hydrobromic acid at room temperature; it recrystallised from alcohol–ethyl acetate as colourless needles, m. p. 236·5—237°. The hydriodide, prepared similarly, had m. p. 248·5—251° (decomp.) (lit. 248°).

(b) *By reduction of* 2-*methyl*-3-*ethylpyrrocoline* (*using platinum oxide*). A solution of the pyrrocoline (5 g.) in acetic acid (20 c.c.) was hydrogenated in the presence of Adams's catalyst (0·4 g.) at room temperature and pressure. The theoretical quantity of hydrogen was absorbed after 5 hrs. After dilution with water, the solution was rendered alkaline, the ammoniacal liquid released extracted into ether, and the product distilled; b. p. 83—85°/12 mm. The colourless mobile liquid obtained possessed a faint violet fluorescence, and gave a positive result in the pine-splinter test, but a colourless melt with oxalic acid. The fluorescence persisted on redistillation (Found : C, 79·1; H, 12·8%). The methiodide, prepared as above, was obtained initially as a jelly-like mass, but recrystallised from alcohol–ethyl acetate as tiny, colourless needles, m. p. 229—229·5° (Found : C, 46·7; H, 7·7; N, 4·5; I, 41·5%). The perchlorate, m. p. 221·5—222° was not depressed in m. p. on admixture with that described above (Found : C, 49·0; H, 8·1; Cl, 13·1. Calc. : C, 49·4; H, 8·2; Cl, 13·3%). Similarly, the hydrobromide, m. p. 234—235·5°, and the hydriodide, m. p. 249—251° (decomp.), did not depress the m. p. of the corresponding derivatives described above on admixture.

Thanks are expressed to Glaxo Laboratories Ltd., Greenford, for generously providing laboratory facilities for two of us (E. T. B. and D. O. H.) and for the supply of materials used in this and the preceding three communications.

Battersea Polytechnic, S.W. 11.
Glaxo Laboratories Ltd., Greenford. [*Received, April 8th*, 1946.]

NOTES.

The 2 : 4-*Dinitrophenylhydrazone of* n-*Valeraldehyde*. By R. S. Airs, D. A. Firth, and P. J. Garner.

Three different values have been recorded for the m. p. of the 2 : 4-dinitrophenylhydrazone of *n*-valeraldehyde : 98° by Allen (*J. Amer. Chem. Soc.*, 1930, **52**, 2955), 106·5—107° by Backer and Haack (*Rec. Trav. chim.*, 1938, **57**, 225), and 88° by Wienhaus and Mucke (*Ber.*, 1942, **75**, 1830). Standard tables of data quote 98°. In the course of work in this laboratory the 2 : 4-dinitrophenylhydrazone of synthetic *n*-valeraldehyde has been prepared.

n-Amyl alcohol was synthesised from *n*-butyl bromide and trioxymethylene by the method given by Freundler and Damond (*Bull. Soc. chim.*, 1906, **35**, 110) for *sec.*-butylcarbinol; it had b. p. 137·5—137·7°/767 mm. Heilbron (" Dictionary of Organic Compounds," Eyre and Spottiswoode, 1943, p. 141) gives b. p. 137°/740 mm. The procedure used by Badin and Pacsu (*J. Amer. Chem. Soc.*, 1945, **67**, 1352) for the production of *iso*valeraldehyde was applied to the above alcohol and yielded *n*-valeraldehyde, b. p. 102·5—103·5°/767 mm. Bruylants and Ernould (*Bull. Acad. roy. Belg.*, 1931, **17**, 1174) give b. p. 102·5—103·0°/760 mm.

The 2 : 4-dinitrophenylhydrazone was prepared by the method of Shriner and Fuson (" The Systematic Identification of Organic Compounds," Wiley and Sons, 1940, p. 143); it separated from methanol in needles, m. p. 107·6° (corr.) (Found : C, 49·9; H, 5·2. Calc. for $C_{11}H_{14}O_4N_4$: C, 49·7; H, 5·3%).

The authors wish to thank the N.V. de Bataafsche Petroleum Maatschappij for permission to publish.—B.P.M.
Research Laboratories, Thornton-le-Moors, Cheshire. [*Received, March 22nd*, 1946.]

The Reaction between Gaseous cyclo*Pentadiene and Benzoquinone*. By Albert Wassermann.

The kinetics of the gaseous diene synthesis *cyclo*pentadiene (a) + benzoquinone (b) ⟶ *cyclo*pentadiene–benzoquinone (c) has been investigated in vessels of " Pyrex " glass between 125° and 155° and at initial pressures between 15 and 25 mm. Under these conditions the reaction is heterogeneous, which is believed to be due to the fact that (a) and (b) are much less polar than the associated species (c). The dipole moment of (a) has not been determined but it cannot be

much more than about 0·3D., since the molecule contains only carbon–carbon and carbon–hydrogen bonds (cf. Smyth, *J. Physical Chem.*, 1937, **41**, 209). The molecule (b) appears to be almost flat (Robertson, *Proc. Roy. Soc.*, 1935, **150**, 106), so the various bond moments should compensate each other and the total dipole moment should be near zero, a conclusion which is not in contradiction with measurements of Hassel and Naeshagen (*Z. physikal. Chem.*, 1929, *B*, **6**, 445), Le Fèvre and Le Fèvre (*J.*, 1935, 1697), Hammick, Hampson, and Jenkins (*J.*, 1938, 1263), and Coop and Sutton (*ibid.*, p. 1269). The dipole moment of (c), on the other hand, is as high as 1·39D. (Le Fèvre and Le Fèvre, *loc. cit.*) owing to the requirements of ring strain keeping the two carbonyl groups rigidly in *cis*-mutual orientation (cf. Fig. 1, *J.*, 1935, 1512). A study of the kinetics of the decomposition of (c) into (a) and (b), carried out by Khambata and Wassermann (*J.*, 1939, 375), led to results which indicate that (c) and the activated complex (ab)* are similar species (cf. Polanyi, *Trans. Faraday Soc.*, 1938, **34**, 143). It is reasonable, therefore, to postulate that in passing from (a) and (b) to (ab)* an increase of polarity takes place. According to this hypothesis the formation of (c) can be compared with the association $NEt_3 + EtI = NEt_4I$ (d), which is also heterogeneous in glass vessels (Moelwyn-Hughes and Hinshelwood, *J.*, 1932, 230) and is supposed to involve relatively strongly polar intermediate configurations (see, *e.g.*, Bell, *J.*, 1943, 632). It follows therefore that in the formation of (c) and (d) the activated complex is characterised by a stronger electrostatic field than the two reactants separately and thus the formation of associated species should be facilitated near a glass surface which can be regarded as a two-dimensional polar liquid. This in turn would give rise to a relatively fast wall reaction which masks the homogeneous association in the gas phase which may be taking place.

It is not within the scope of this paper to compare the mechanism of the formation of (c) and (d) with that of gaseous associations, or of reactions of the type A + B = C + D involving rate-determining steps of unknown stoicheiometric equation. Reference is made, however, to the previously investigated gaseous bimolecular diene syntheses (for a list, see *J.*, 1939, 366) which are all homogeneous. These processes either involve participants which are hydrocarbons, or else one of the reactants is a hydrocarbon and the other an aldehyde, and there is no effect which could be made responsible for a marked difference of polarity between the initial state and the activated complex. It is understandable, therefore, that the polar wall of the reaction vessel does not substantially enhance the formation of the activated complex, and it is believed that for this reason the heterogeneous association does not become predominant.

Experimental.—The rate measurements were carried out by using the apparatus described by Benford and Wassermann (*J.*, 1939, 366). The two 6-l. "Pyrex" flasks were first filled with vapour of carefully purified (b), and then with redistilled gaseous (a), the initial pressure of which was determined by extrapolating the total pressure to the time of mixing and subtracting from this the pressure of (b); the time of mixing was taken to be that when one half of (a) had been distilled into the reaction vessels. It was ascertained that neither the tap grease nor the mercury had a detectable influence on the kinetics. After each experiment the reaction mixture was distilled out and the substances thus obtained were jointly purified by fractional recrystallisation from hexane. *cyclo*Pentadiene–benzoquinone could be isolated and was identified by mixed m. p. In attempting to characterise the rate of addition of gaseous (a) to (b) by second-order velocity coefficients, v, it was found that at 125° and 135° the values of v increased with time, but at 145°, 153°, and 155° a decrease took place. Typical experiments in "empty" vessels are shown in Table I. The initial pressure of (b) was 5·9 mm. at 125° and 10·7 mm. at 153°.

TABLE I.

125°	Time (mins.)	0	8	13	18	28	43
	Pressure (mm.)	14·6	12·9	12·0	11·0	9·6	8·5
	v (l. g.-mol.$^{-1}$. min.$^{-1}$)	—	130	144	184	264	400
153°	Time (mins.)	0	10	20	30	100	
	Pressure (mm.)	22·0	20·9	20·0	19·5	17·8	
	v (l. g.-mol.$^{-1}$. min.$^{-1}$)	—	26	26	24	14	

The trend in v is probably due to condensation of the product molecule and to consecutive, simultaneous, and reverse processes taking place. In order to compare the rate under different conditions the observed values of v were extrapolated to zero conversion. The velocity coefficients v_0 so obtained are given in Table II where (*p*) denotes a packed and (*e*) an empty vessel. The packed vessels were filled with tubes of "Pyrex" glass, thereby providing a surface-volume ratio 5 times greater than in the empty vessels. The statement that the formation of gaseous (c) is heterogeneous is based on the observation that the v_0 values in packed vessels are larger than in empty vessels and that v_0 decreases with increasing temperature. A negative temperature coefficient is found also in many other heterogeneous gas reactions.—THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES, UNIVERSITY COLLEGE, LONDON. [*Received, March 7th*, 1946.]

TABLE II.

Temp.	Initial press. (mm.). $C_6H_4O_2$.	C_5H_6.	v_0.	Temp.	Initial press. (mm.). $C_6H_4O_2$.	C_5H_6.	v_0.
125°	8·5	13·5	400 (*p*)	145°	11·2	11·2	44 (*e*)
	8·6	11·8	100 (*e*)	153	10·7	11·1	28 (*e*)
	5·9	8·7	100 (*e*)	153	10·7	11·1	40 (*p*)
136	10·0	9·9	60 (*e*)	155	9·6	11·4	30 (*e*)

Metal Sulphide Catalysis of a Simple Cracking Reaction. By B. S. KHAMABATA and ALBERT WASSERMANN.

THESE experiments deal with the reverse diene synthesis: di*cyclo*pentadiene = 2 *cyclo*pentadiene, in which the rupture of the carbon–carbon bonds is accompanied by a rearrangement of double bonds without a release or uptake of hydrogen. We have found that on addition of certain metal sulphides a heterogeneous reaction is superimposed upon the unimolecular homogeneous decomposition of di*cyclo*pentadiene, the kinetics of which we have already studied (*J.*, 1939, 375). The present measurements were all done with 25 c.c. of 0·75M-di*cyclo*pentadiene in paraffin, at 155° and at atmospheric pressure, the activities of the contact substances being characterised by first-order catalytic initial velocity coefficients, V_c, which were obtained from $V_c = V_c' - k_0'$, where k_0' is the unimolecular initial rate constant of the homogeneous reaction and V_c' is the overall initial rate coefficient. The V_c values in the accompanying table all relate to 0·6 g. of contact material, not to unit surface area; these coefficients are merely used as a convenient comparative measure of the catalytic activity of the various sulphides, but there is no experimental evidence to show that the heterogeneous decomposition of di*cyclo*pentadiene is a first-order reaction.

It may be noted that, out of 14 black or brown sulphides, only one had no measurable catalytic effect, whereas all the yellow and white sulphides were inactive; but further work is required before this dependence on colour can be regarded as anything more than fortuitous within the range of sulphides investigated.

Influence of metal sulphides on the rate of decomposition of dicyclopentadiene.

(Solvent, paraffin; temperature, 155°; initial concn. of $C_{10}H_{12}$ = 0·75 g.-mol./l.)

Contact material.	$V_e \times 10^3$ (min.$^{-1}$).	Contact material.	$V_e \times 10^3$ (min.$^{-1}$).
CuS (comml.)	9	NiS	8
CuS (specially prepd.*)	4—7	SnS	8
CuS + 20% $CuSO_4,5H_2O$	5	Tl_2S	4
CuS + 20—60% S	5—6	PbS	7
CuS (pptd. on surface of animal charcoal †)	6	HgS	7
CuS (pptd. on surface of $CaCO_3$ †)	9	Bi_2S_3	5
Cu_2S	5	MoS_2	<0·3
Pyrites	2	ZnS	
FeS	8	SnS_2	
Copper pyrites	5	As_2S_3	
Potassium ferric sulphide	4	SrS	
Ag_2S	2	CdS	

* See below, Nos. 1—6.

† Animal charcoal and calcium carbonate alone are without measurable activity.

Under the experimental conditions k_0' is 2·0 ± 0·1 × 10^{-3} min.$^{-1}$, and comparison with the tabulated V_e values shows that with the catalytically active sulphides the initial rate of the cracking reaction is increased by 100—350%.

Experimental.—Dicyclopentadiene was purified as before (*loc. cit.*) and the paraffin was from the stock previously used. All the present measurements were done by the " second method " (*loc. cit.*, p. 379), the dimensions of the apparatus (*ibid.*, p. 380), stirring speed, and temperature of the gas burette being unaltered. The course of a typical experiment with and without a catalyst was as follows :

	Time (mins.)	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
C_5H_6, c.c., collected at 750 mm. pressure	With 0·6 g. of comml. CuS	5·2	9·0	12·2	15·2	17·8	19·6	21·6	23·2	24·6	26·0
	Without catalyst	2·0	3·8	5·2	6·4	7·6	8·6	9·4	10·2	11·0	11·6

In control experiments in which the contact materials without dicyclopentadiene were stirred in paraffin suspension, no detectable gas evolution occurred.

The various cupric sulphide preparations referred to in the table ($V_e \times 10^3$ = 4 — 7 min.$^{-1}$) were made as follows : (1) Hydrogen sulphide was bubbled at room temperature through a 0·9M-cupric sulphate solution which was 0·1M with respect to hydrochloric acid; when all the copper was precipitated, the sulphide was centrifuged off, washed with water, and dried for 8 hours at 90° in air. (2) This was precipitated as sample (1), but the drying was done in a vacuum at room temperature; the dried sample was exposed at room temperature for 70 hours to air. (3) This was precipitated as sample (1), but was washed on the centrifuge with dilute acetic acid, saturated with hydrogen sulphide; the drying was done at room temperature in a vacuum. (4) This was precipitated as sample (3), but the cupric sulphate solution did not contain hydrochloric acid. (5) This was precipitated by slowly adding a 0·2M-sodium sulphide solution to an equivalent volume of 0·2M-cupric sulphate, the precipitate being washed and dried as sample (3). (6) This was prepared as sample (3) except that water was used for the washing.

The mixtures of cupric sulphide with cupric sulphate or sulphur were made by using sample (2), the dry components being ground together. The cupric sulphide–animal charcoal and the cupric sulphide–calcium carbonate catalysts were made as follows : 10 G. of animal charcoal (A.R.) or 10 g. of finely powdered calcium carbonate were stirred, at room temperature, for 45 mins. with 120 c.c. of 0·8M-cupric sulphate solution which was 1M with respect to hydrochloric acid; hydrogen sulphide was then passed through the suspension for ½ hour, and the mixture filtered, the residue being dried under the same conditions as sample (1).

The ferrous sulphide was made by precipitating a 0·1M-ferrous sulphate solution with an equivalent quantity of 0·1M-ammonium sulphide; the precipitate was washed with dilute acetic acid saturated with hydrogen sulphide, and dehydrated by heating to 120° under a layer of paraffin. The suspension of the sulphide in paraffin was added to the dicyclopentadiene after an aliquot portion of the suspension had been analysed.

The other sulphides were all finely powdered, passed through a 50-mesh sieve, and dried in a vacuum at room temperature to constant weight.

No attempt was made to investigate the influence of temperature or concentration of dicyclopentadiene on the rate of the catalysed decomposition, the accuracy of the V_e values being only ±15%. A few tests were made, however, in which the weight of the catalyst was varied while everything else was kept constant : V_e increased in all cases with increasing weight of sulphide; *e.g.*, with 0·2, 0·6, and 3·6 g. of a commercial cupric sulphide the V_e values were respectively 5 × 10^{-3}, 9 × 10^{-3}, and 35 × 10^{-3} min.$^{-1}$.—The Sir William Ramsay and Ralph Forster Laboratories, University College, London. [*Received, March 22nd*, 1946.]

OBITUARY NOTICE.

AUGUSTE BÉHAL

1859—1941

AUGUSTE BÉHAL was born of farming stock at Lens on 29th March, 1859, and received the greater part of his secondary education at the Collège de Béthune. His specialisation in chemistry and particularly organic chemistry, like that of so many eminent French chemists, followed the long training and qualification as " Pharmacien ".

After the completion of his training with distinction at the famous École de Pharmacie, Béhal in 1884 began his study under Friedel at the Sorbonne of ethylenic hydrocarbons, the subject of his thesis for the Doctorat-ès-Sciences in 1889. In the meantime he filled various appointments at well-known hospitals at which he had as pupils such men as Moureau, Desgrez, Blaise, Valeur, Tiffeneau, and Sommelet.

In 1890, at the École de Pharmacie, Béhal started his public or extra-mural lectures on Organic Chemistry which were immediately an outstanding success. He continued this course for several years even without remuneration. It led to the publication in 1896 of his " Traité de Chimie organique d'après des théories modernes " which established his reputation as a leader in organic chemistry in France, and he was given the title of Professor without assignment to any particular school.

In 1892, Béhal was one of the French delegates to the historic Geneva Conference for the Reform of the Nomenclature of Organic Chemistry; but any substantial recognition of his increasing eminence as an organic chemist did not arrive until he was appointed " Maître des Conférences de Chimie organique " to Friedel at the Sorbonne in 1898. On Friedel's death in 1899, Béhal remained in charge until Haller was appointed to the vacant chair, and he himself had to be content with the appointment as Professor of Toxicology at the École de Pharmacie. It was not until six years later that Béhal was appointed full Professor of Organic Chemistry at the École de Pharmacie, succeeding Jungfleisch who had migrated to the newly instituted Collège de France. For thirty years, Béhal's department in the Faculté de Pharmacie was, under his inspiration and organisation, an important centre of teaching and research in organic chemistry. Béhal was Honorary Secretary of the Société chimique de France from 1893 to 1911 when he was elected President. He was also President of the Société de Pharmacie and, in 1937, President of the Société de Chimie industrielle.

Béhal was elected Member of the Académie de Médicine in 1906 and President in 1922. In 1921 he was elected into the Académie des Sciences in the Chemistry Section, and in 1939 he had the distinction of election to the Presidency. He was created Grand Officier de la Légion d'Honneur in 1929. He became an Honorary Fellow of the Chemical Society in 1933.

During the 1914—1918 War, Béhal was Director of the Department of Chemical Products charged with the organisation of the production of pharmaceuticals, toxic materials, dyestuffs, and numerous chemical materials urgently needed in the national emergency. One of the offices of the liaison staff of the British Chemical Warfare Department was established at the École de Pharmacie, and it was there that the writer first met Béhal and came to enjoy his friendship and that of his charming wife. Béhal's rugged appearance was in keeping with his forthrightness, his command of affairs, his great sense of humour, and his calmness in all circumstances. It was good to know him. Béhal's war-time service convinced him of the importance of the establishment of a suitable centre of documentation for chemistry and the maintenance of intimate relationship between academic research and industry, and he devoted himself with others to the establishment of the Maison de la Chimie. It was Béhal who secured the active support of Sir Robert Mond who with Lady Mond became the largest private benefactor. The Maison de la Chimie is almost a monument to Béhal.

Béhal's scientific work covered a wide field. Problems connected with unsaturation of complex acetylenic and ethylenic hydrocarbons were for a long time under investigation by Béhal and his pupils. In this connection, and as an example of the neatness of Béhal's work, he introduced the use of " urea chloride " (carbamyl chloride, $NH_2 \cdot CO \cdot Cl$) as a convenient means of the addition of hypochlorous acid to ethylenic hydrocarbons and, with Detoeuf, prepared numerous glycol chlorohydrins. Similarly, his identification of alcohols by means of their allophanates, $H_2N \cdot CO \cdot NH \cdot CO_2R$, had a considerable influence in elucidating problems of constitution in the terpene series (*e.g.*, carvomenthol and *iso*pulegol). Again, his introduction of the use of thionyl chloride for the preparation of acid chlorides and chlorine derivatives has been of inestimable service to organic chemists; but he also employed it in connexion with his terpene investigations by obtaining, from camphoroxime, β-campholenic acid which he converted into campholene. In his studies in the terpene series, Béhal modified the Sabatier–Sanderens method of reduction by using a nickel catalyst. On applying this to α-terpineol, he obtained a dihydro-α-terpineol isomeric with that obtained by Wallach; these two compounds were later shown to be *cis-trans* isomerides.

Following Gerhardt's classical investigations Béhal made a study of mixed anhydrides, those from formic acid showing the remarkable property of decomposing with evolution of carbon monoxide when allowed to react with a tertiary amine. Another isolated and neat piece of work, carried out with Choay, was the preparation and proof of the constitution of chloralimide, $(CCl_3 \cdot CH{:}NH)_3$, and still another was the preparation of guaiacol for the first time in the crystalline condition which contributed to its extended therapeutic application. With Sommelet and Tiffeneau, Béhal explored the use of the Grignard reaction for the preparation of certain

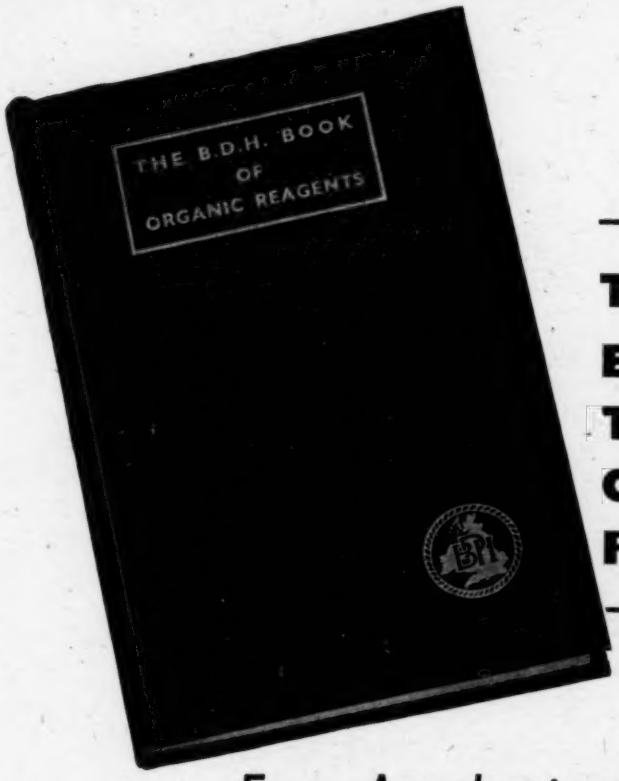
[*To face p.* 1092.

glycol ethers, easily hydrolysable to dialkylacetaldehydes, and the preparation of phenyl ethers, incidentally proving the structure of anethole. An earlier investigation, with Auger, on the action of malonyl chloride on aromatic hydrocarbons in the presence of aluminium chloride, led to the production of β-diketones of the type, $R{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}R$, which had "acid" properties and formed metallic derivatives; by decomposition with concentrated alkalis these β-diketones proved to be a convenient source of ketones and acids of the general types, $R{\cdot}CO{\cdot}Me$ and $R{\cdot}CO_2H$, respectively.

Auguste Béhal died on 2nd February, 1941, at Mennecy (S. et O.). He never doubted that France would regain her liberty and greatness.*

C. S. GIBSON.

* The writer is greatly indebted to MM. André Kling and M. Sommelet and to (the late) M. Damiens for information regarding certain details of Béhal's career. The photograph is taken from a commemorative medal struck at the time of Béhal's retirement.



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